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## SYMPTOMATOLOGY OF MYXEDEMA

ITS RELATION TO METABOLIC LEVELS TIME INTERVALS  
AND RATIONS OF THYROID

J H MEANS, M D

AND

J LERMAN, M D

BOSTON

Our excuse for introducing for discussion so time-worn a subject as the symptomatology of myxedema is that the recent introduction of artificial hypothyroidism as a form of therapeutics makes the topic once more timely. If one is to steer successfully between the Scylla of congestive heart failure or angina pectoris on the one hand and the Charybdis of myxedema on the other, some precise information concerning the relation of symptoms to metabolic rates, time intervals and thyroid rations becomes necessary. Coordinated clinical observations and determination of the metabolic rate on patients with myxedema have been accumulating in our clinic over a period of twenty years (more than two hundred and forty cases). This material provides an excellent source of information. Many of our patients have been under observation year after year, so that our estimate of the relation of symptoms to the height of the metabolic rate is based on long periods in which the level has been steady.

Recently we saw our first patient with myxedema, Mrs D whose case was reported fully by Means and Aub<sup>1</sup> in 1919 and who first came under observation in October 1914, when she was 57 years old. She had then had myxedema for six years but had taken no treatment. For just less than twenty years she has steadily received a thyroid ration and has remained essentially in perfect health. When we saw her on April 3, 1934, she was an alert, active woman of 77.

During this rather prolonged period of observation of patients with myxedema certain facts have strongly impressed us. One is that the people in whom the disease spontaneously develops possess for the most part, what Draper<sup>2</sup> might call a characteristic physical and mental panch

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From the Thyroid Clinic of the Massachusetts General Hospital

Read before the Association of American Physicians Atlantic City N J  
May 2, 1934

1 Means, J H., and Aub, J C. The Basal Metabolism in Hypothyroidism  
*Arch Int Med* 24 404 (Oct) 1919

2 Draper, G. Disease and the Man, New York The Macmillan Company  
1930

Physically they tend to be broad-shouldered, short-necked and stocky. Mentally they are characterized by a sunny disposition and fine sense of humor. They are what the Victorians would have called amiable—amazingly so.

For the purposes of the present study, fifty of the group were made the subject of careful scrutiny. The facts which emerged have been sublimated in chart 1. This figure is a generalization. It portrays approximately what happens in most cases, not precisely what happens, unless by chance, in any single case. It shows, we believe, with a fair

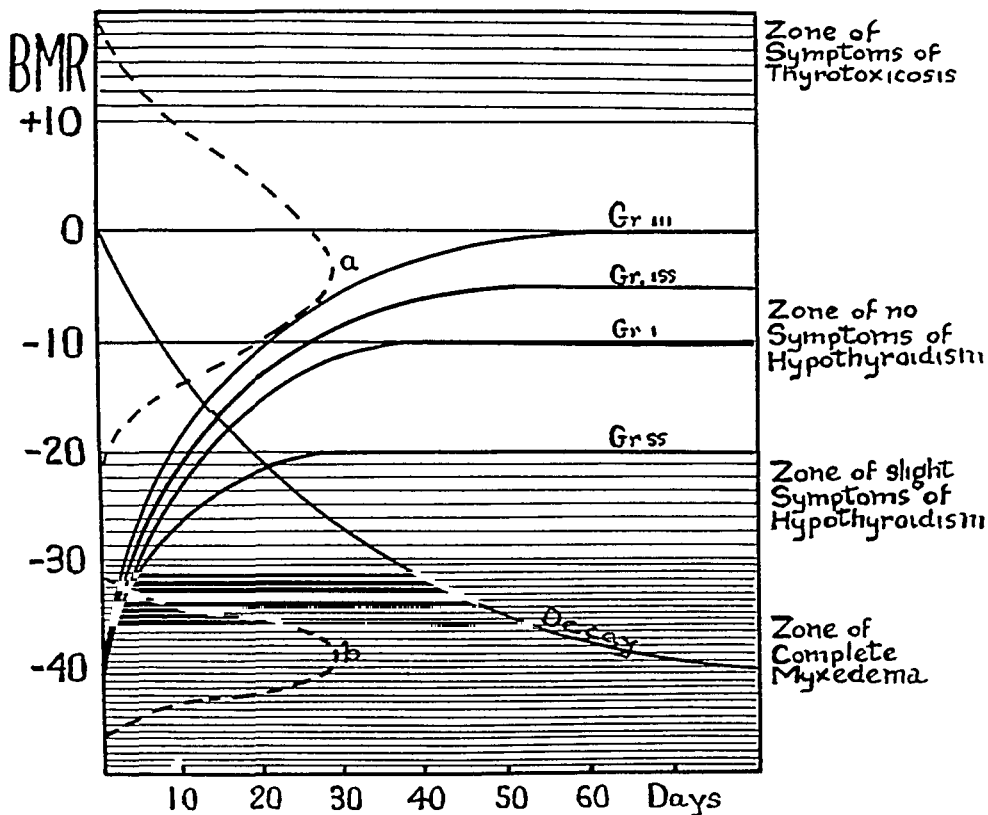


Chart 1—Diagram showing the approximate relationships between metabolic levels, symptoms and thyroid ratios. The dosage is indicated in grains of thyroid, U S P, given once a day. The curves, so labeled, indicate what may be expected to happen in the way of calorific response when the several ratios are given to patients with complete myxedema. The curve labeled decay indicates the metabolic response which may be expected when one discontinues the administration of thyroid to a patient with myxedema whose metabolic rate was maintained at a standard level or when one completely extirpates the thyroid gland of a person with a standard metabolic rate. The frequency curves, plotted against the basal metabolic rate, at the left are (a) for persons with no thyroid disease and (b) for patients with spontaneous myxedema.

degree of accuracy, the results that one may expect in treating patients with hypothyroidism and how to employ symptoms as a guide.

In the first place, it became clear that the true basal metabolic level of untreated patients with fully developed myxedema is far more constant than that of persons with intact thyroid glands. Epstein called attention to this fact and referred to the metabolism of the person with no thyroid gland as the true biologic basal or "fundamental" metabolism, a foundation on which all higher rates are erected. We agree. On the left side of chart 1, plotted against the metabolic rate, are two frequency curves, showing the basal metabolic rates (*a*) of persons with no thyroid disease and (*b*) of persons with myxedema. It will be noted that *a* has a far wider base than *b*. That is to say, the basal metabolic rates of persons with an intact thyroid gland are far more variable than those of persons with no thyroid gland.

The next point of interest is that the presence or absence of symptoms is closely related to the level of metabolism. In chart 1 are shown several zones which indicate the general nature of the relationship. Below minus 30 (speaking always in terms of the Aub-DuBois standards) is the zone of complete myxedema. One seldom finds fully developed symptoms of hypothyroidism unless the metabolic rate has entered this region. The converse is not true, as will be noted later, because the metabolic rate falls more rapidly than symptoms develop. From minus 20 to minus 30 is the region in which one usually finds slight symptoms of hypothyroidism. Above minus 20 one seldom observes them. When the metabolic rate has been forced upward by the administration of thyroid to the neighborhood of plus 10, symptoms of hyperthyroidism not infrequently make their appearance.

We have given special attention to the problem of the level at which a given ration of thyroid will hold the metabolic rate of patients with myxedema. The four curves shown in chart 1 indicate our experience. The dosage is in terms of thyroid, U. S. P. This must be emphasized, because the brands of thyroid on the market do not all conform to the requirements of the pharmacopeia for iodine and therefore differ in calorogenic action.<sup>4</sup> The ascending limbs of the curves indicate, in days, approximately the time required for the metabolic rate to become steady. The curves are smoothed from the numerous assays we have made of thyroid preparations. The levels themselves are taken from the observations on patients treated for a long time. The results show that  $\frac{1}{2}$  grain (32.4 mg.) of thyroid once a day will maintain the basal rate of most patients with myxedema at a level of about minus 20.

3 Epstein, A. A. The Reciprocal Functions of the Thyroid Gland and Iodine. Their Relation to the Fundamental Metabolism of the Body, Libman Anniversary Volumes, New York, International Press, 1932, vol. 1, p. 365.

4 Lerman, J., and Salter, W. T. The Maintenance Requirements of Myxedema Patients. Clinical and Chemical Assay of Commercial Thyroid Preparations, *J. Pharmacol. & Exper. Therap.* **50**: 298, 1934.



which, it should be noted, is about the upper border of the zone of slight symptoms. One grain (64.8 mg) maintains the rate at about minus 10,  $1\frac{1}{2}$  grains (97.2 mg), at about minus 5, and 3 grains (194.4 mg), at about the standard level.

For comparison we have inserted also in chart 1 the so-called curve of decay of the hormone. This represents the effect on the metabolic rate of sudden elimination of the source of thyroxine. It is what may be expected if one suddenly stops the thyroid ration of a patient with myxedema whose rate has been maintained at a standard level, or if the thyroid gland is completely extirpated. There are a number of such curves in the literature,<sup>5</sup> and they are surprisingly alike in contour. The important point about them is that it takes seventy or more days to attain the metabolic level of complete athyreosis.

The nature of the curve of decay led to a study of the rate of development of symptoms. Regarding this, some interesting points were found. We had been aware for a number of years, as doubtless had others doing the same sort of work, that in the development of the picture of hypothyroidism the fall in the metabolic rate precedes the development of clinical symptoms and signs. For example one patient (Mrs. B.) who was first seen with fully developed myxedema was given 10 mg. of thyroxine in one dose intravenously, for purposes of assay. This raised the basal metabolic rate from a level of minus 45 to one of about minus 6 in seven days. The metabolic rate was back in the minus thirties within a month, but it was about three months before any symptoms of importance appeared. This result was duplicated in several other patients, and is similar to the effect observed in artificial hypothyroidism.<sup>6</sup> This lag of symptoms behind the change in the metabolic rate is probably to be explained by the fact that although the symptoms and the metabolic rate are unquestionably related, the symptoms are due in large measure to the lack of other than the calorogenic action of thyroxine. Indeed, with the evidence now at hand, it seems unlikely that more than chilliness and decreased sweating can be explained by a low metabolic rate alone. The other signs of classic

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5 Boothby, W. M., Sandiford, I., Sandiford, K., and Slosse, J. The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, *Tr. A. Am. Physicians* **40** 195, 1925. Thompson, W. O., Thompson, P. K., Brailey, A. G., and Cohen, A. C. The Calorogenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, *J. Clin. Investigation* **7** 437, 1929.

6 Gilligan, D. R., Volk, M. C., Davis, D., and Blumgart, H. L. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. VIII. Relationship Between Serum Cholesterol Values, Basal Metabolic Rate and Clinical Aspects of Hypothyroidism, *Arch. Int. Med.* **54** 746 (Nov.) 1934.

myxedema have to do with other actions of thyroxine, for example, its action on the distribution of body water, salt and protein and on the rate of growth of the tissues

In the matter of symptoms of spontaneous myxedema, we became convinced that truly full-blown athyreotic cachexia requires a long period of time to develop. After the metabolic rate drops into the zone of symptoms, a slow evolution takes place over a period of years. Since in spontaneous myxedema the lesion found is total atrophy of the thyroid gland, one must infer that in the beginning of the disease a period of partial athyreosis exists. However, experience with induced athyreosis shows that myxedema is not produced unless the gland is totally removed. A small fragment is capable of supplying an adequate or nearly adequate amount of thyroxine. Therefore, it may fairly be inferred that the symptoms of spontaneous myxedema come on only after the atrophy of the gland has become complete. The period of partial athyreosis is passed in the asymptomatic zone of metabolism.

Though once in a great while a person may be found with a moderately low basal metabolic rate, say minus 20, in whom true myxedema is actually developing, for the most part persons with such a rate do not have hypothyroidism but owe their low metabolic rate to some other mechanism. We interpret our experience as signifying that a person either does or does not have myxedema. Borderline or half-way types of hypothyroidism, we think, exist either not at all or rarely. Hypometabolism is no more synonymous with hypothyroidism than fever is synonymous with measles. Indeed, we have had patients with a metabolic rate as low as minus 40 who did not show clinical signs of myxedema and whose low rate was in all probability not related to disturbance in the thyroid gland.

The length of time required to make the diagnosis of myxedema next engaged our attention. It is unfortunate when the diagnosis of a curable disease is missed, particularly if, when untreated, it ultimately causes death, as is the case with myxedema. In forty-three of the fifty cases analyzed the history permitted an estimate of the length of time the disease existed before the diagnosis was made. These data are given in chart 2. Two patients undoubtedly had myxedema for fifteen years before it was recognized. One of them was seen last winter in consultation with Dr. J. H. Townsend at the Cambridge Hospital. She was a woman who was brought to the hospital for the first time in a lethargic state, nearly moribund. Dr. Townsend recognized the condition as myxedema and invited us to see her. Thyroxine was given intravenously but it was too late, she died within twelve hours after treatment was begun. The diagnosis of myxedema should be easy, but chart 2 indicates that nevertheless it often is missed. Of the wrong diagnoses made in these cases, anemia was first, then Bright's disease. In two cases, because

of menorrhagia (which is the characteristic menstrual change in women in whom myxedema develops prior to the menopause) a diagnosis of pelvic tumor was made, and the patients sent to a hospital for gynecologic diseases for operation. At this hospital the right diagnosis was made, and the patients were sent to us. In a third recent case, not included in this series, there was a history of hysterectomy for menorrhagia. The circumstances were such that we suspected that the menorrhagia was caused by myxedema and that the hysterectomy was not necessary.

We hope that the information contained in chart 1 may be helpful in the management of either spontaneous or induced hypothyroidism. It

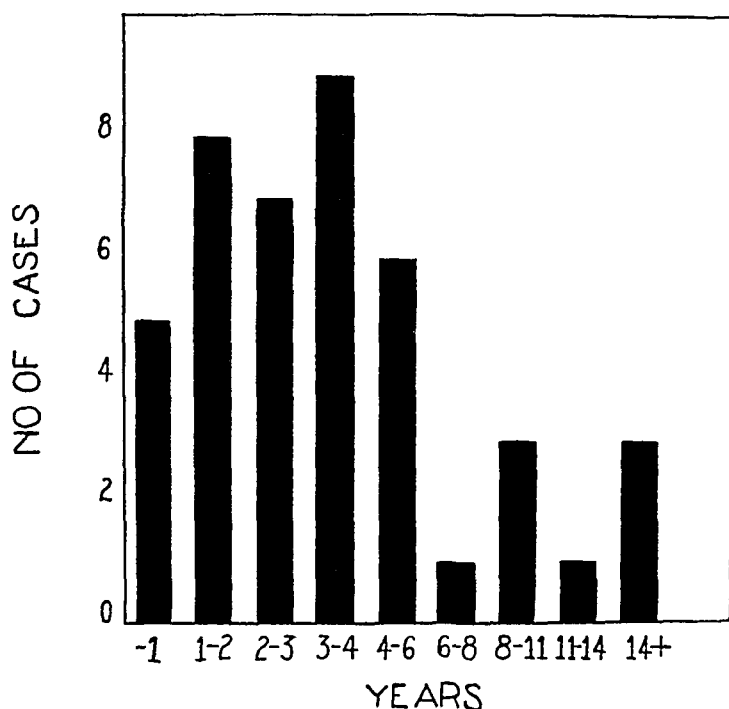


Chart 2—Time elapsing in cases of myxedema before a diagnosis was made as estimated in forty-three cases

is perhaps more instructive in relation to the latter condition. It provides an answer to the question so commonly asked: "What is the sense of removing the thyroid gland to cure heart disease when it will cause myxedema and make the heart worse?" The diagram indicates that if the metabolic rate of the patient with cardiac disease is at the standard level or higher, a 20 or 25 point drop can be effected with little or no symptoms of hypothyroidism. This may be sufficient to make the difference between cardiac decompensation and compensation. A method may some day be found to lower the metabolic rate to minus 40 without producing myxedema, then the patient with cardiac disease may rejoice. At the moment the patient may be thankful for the 20 point drop in the rate which is now possible.<sup>6</sup>

# GASTRIC MUCIN TREATMENT FOR PEPTIC ULCER

A REPORT BASED ON QUESTIONNAIRES

SAMUEL J FOGELSON, M D

CHICAGO

My interest in the rôle played by mucin in the physiology of the gastro-intestinal tract and the management of gastroduodenal ulceration was stimulated by Lim's publication, "On the Relationship Between the Gastric Acid Response and the Basal Secretion of the Stomach" <sup>1</sup> At the lower secretory rates the concentration of mucus is undoubtedly higher than during the more active phases of gastric secretion Many clinicians have noted a decreased secretion of mucus in patients with ulcer <sup>2</sup> It is likewise noteworthy that the many patients with ulcer rarely return to a normal basal secretory state My objective, therefore, was to feed mucin to patients with ulcer in an attempt to correct the mucin deficiency as well as to restore normal basal secretory rates By 1929 I had prepared a gastric mucin adequate for experimental and clinical investigation The first clinical report on the treatment of gastroduodenal ulceration with gastric mucin followed in 1930, when the encouraging results in 12 patients were described <sup>3</sup> Experimental investigation by Ivy <sup>4</sup> on the control of experimental ulcer by mucin followed, affording further physiologic support for continuing my clinical research on the management of peptic ulcer with gastric mucin

To obtain an accurate evaluation of mucin as well as to eliminate personal bias, there was established by the Northwestern University Medical School a Gastric Mucin Committee Under the direction of this committee the following units were established for the investigation of the treatment of gastroduodenal ulcerative disease with mucin at St Luke's Hospital, Chicago, under the direction of Dr N C Gilbert and Dr C F G Brown, <sup>5</sup> at the Passavant Hospital, Chicago.

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From the Department of Experimental Surgery, Northwestern University Medical School

1 Lim, R K S On the Relationship Between the Gastric Acid Response and the Basal Secretion of the Stomach, *Am J Physiol* **69** 318 (July) 1924

2 Kaufman, J Lack of Gastric Mucus and Its Relation to Hyperacidity and Gastric Ulcer, *Am J M Sc* **135** 207, 1908

3 Fogelson, S J The Treatment of Peptic Ulcer with Gastric Mucin, *J A M A* **96** 673 (Feb 28) 1931

4 Ivy, A C The Physiology of Mucous Secretion with Some Experimental Results on the Prevention of Ulcer with Gastric Mucin, *Nebraska State M J* **17** 317 (Aug) 1932

5 Brown, C F G, Cromer, S P, Jenkinson, E L, and Gilbert, N C Mucin Therapy for Peptic Ulcer, *J A M A* **99** 98 (July 9) 1932

under the direction of Dr A J Atkinson,<sup>6</sup> and at the Wesley Memorial Hospital, Chicago, under my own charge. These three groups treated over 600 patients with encouraging results, confirming, in general, my original report.

In addition, mucin was made available to all physicians interested, with the request that they cooperate with the Gastric Mucin Committee in reporting the type of condition treated and the results obtained. The present report, based on the results obtained by clinicians with little or no previous experience with mucin therapy, should be valuable in determining the effectiveness of mucin therapy.

#### DATA FROM QUESTIONNAIRES ON 555 CASES

During the last three years there have been reported to the Gastric Mucin Committee approximately 555 patients who have been followed for periods varying from six months to three years. These patients were divided into two groups: (1) a group of patients in whom it had been possible to control the symptoms by the accepted orthodox methods, and (2) another group in which the types of therapy previously used afforded no relief. The cases in the latter group were classified as "intractable." The committee decided that unless mucin should prove of value in the treatment of this group with "intractable" cases of ulcer, it deserved no place in the medical management of ulcer and that its manufacture as well as its distribution would be stopped. To simplify the treatment all clinicians interested in this work were supplied with instructions, describing the dosage as well as the simplest and most effective technics of administration of mucin. To facilitate the reporting, these clinicians were likewise furnished summary sheets for a brief history stressing classification of the type of lesion treated, the roentgenographic findings, the history of recurrences, the incidence of hemorrhage, previous surgical procedures and the effect of former treatment. The results obtained with mucin therapy were recorded on a progress sheet which included the more significant symptoms and the time required for their control. Table 1 shows a typical progress record from a clinician cooperating in this study.

Much valuable information was acquired about effective dosage, the mode of administration and the occurrence of unfavorable effects. Such data were of real value in determining just what results may be expected from mucin therapy in the treatment of patients with ulcer, particularly of patients who previously did not respond to medical management or to surgical therapy. Practically no patients were hos-

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<sup>6</sup> Atkinson, A J. Gastric Mucin in the Treatment of Peptic Ulcer, *J A M A* **98** 1153 (April 2) 1932.

TABLE 1—Report Showing Typical Response to Mucin Therapy by Patient with Uncomplicated Gastric Ulcers'

Name of Patient E L			Name of Physician O L A , Ville Platte, La																														Diagnosis		Date of monthly report											
1932 April																																			May 12, 1933											
Day of month			12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10	11	12													
Time of muen treatment			100 Gm daily in 1½ quarts milk and cream divided into 12 hourly doses																																											
Nausea		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Vomiting		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Pyrosis		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Eruetation		0	0	0	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Belching		+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Flatulence		+	+	+	+	+	+	+	+	+	0	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Epigastric pain		+	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Lpig'astric discomfort		+	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Epigastric tenderness		+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Anorexia		+	+	+	+	+	+	+	+	+	+	+	0	0	0	+	+	0	0	0	0	+	0	0	0	0	0	+	0	0	0	0	0													
Nocturnal pains		0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Hunger pains		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Constipation		+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	+	+	+	+	0	0	+	0	0	0	+	0	0													
Diarrhea		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Hematemesis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Melena (benzidine)		+	+	+	+	+	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0													
Gastric analysis																																														
Free hydrochloric acid		50						40									35																25													
Total acids		90					60										55																55													
Red blood count		3,500,000																																4,000,000												
Hemoglobin		70%																																75%												
Weight		130																																140												
Belladonna dose		None given						133									135																136													

\* This is the type of record used by the cooperating clinicians in sending to the Gastric Mucin Committee reports on the progress of their patients

pitalized, because previous experience with ambulatory treatment had proved relatively satisfactory. Patients were instructed to take mucin suspended in a mixture of milk and cream at frequent regular intervals throughout the day. As a rule the average patient can tolerate from 80 to 100 Gm. of dry mucin powder, which to acutely ill patients was administered in hourly doses. Whenever possible the administration of mucin was continued for at least six months, the dosage being reduced during the last three months.

The difficulties of taking mucin by the patient with ulcer have been grossly exaggerated. With no personal experience on their part, the physicians of the 555 patients, following the instruction sheets furnished by the Gastric Mucin Committee, reported no grave difficulty in the protracted administration of the product. To prescribe mucin without proper instruction as to how it is to be taken is to tempt failure. When in doubt, my patients are given a demonstration by a competent dietitian, taste the mixture properly prepared and thus are psychologically prepared against failure. The diet was limited to the customary bland diet for patients with ulcer. Complicating gastro-intestinal conditions such as spastic colitis or constipation were treated by appropriate measures.

#### RESULTS

The response to mucin therapy was classified as (1) complete relief of symptoms, (2) partial relief, and (3) absolute failure. Recurrences were included in the group of failures because temporary alleviation of symptoms could hardly be considered more than a frank failure. The reports on a total of 555 patients with an average duration of symptoms of slightly less than eight years were submitted to the Gastric Mucin Committee by clinicians cooperating in this investigation. The greater number of the patients had responded unsatisfactorily to previous therapy, 106 had been submitted to surgical procedures with post-operative recurrence of symptoms, and 220 gave a history of repeated massive hemorrhages. Of the 555 patients treated for periods varying from six months to three years, 348, or 62.7 per cent, were rendered free of symptoms, 114, or 20.5 per cent, were partially improved and 93, or 16.8 per cent, failed to be relieved. In the group of 93 patients who failed to respond to mucin therapy, there were 32 true failures or recurrences. The remaining 61 were patients who for various reasons would not continue the treatment for an adequate period or in whom complicating factors prevented the possibility of obtaining symptomatic relief. Deducting these 61 patients from the total, there remain 494, of whom 348, or 70.5 per cent, were completely relieved of all symptoms, 114, or 23 per cent, were improved and 32, or 6.5 per cent, failed to be relieved.

The types of ulcer treated were as follows

	No Patients
Duodenal ulcers	408
Gastric ulcers	125
Gastrojejunal ulcers	22

One hundred and six patients had had previous operations followed by recurrences and 220 had had previous hemorrhage. In some of these patients an occasional symptom persisted for months after the beginning of treatment with mucin, but as a general rule all symptoms were completely controlled within one week.

*Group with Intractable Ulcer*—Of the 555 cases, 226 were classified as intractable by the patients' own clinicians because they did not respond to the orthodox types of treatment. Surgical treatment had

TABLE 2—*Duration of Symptoms After Institution of Mucin Therapy*

Symptoms	Days
Nausea	31
Vomiting	12
Pyrosis	56
Epigastric pain	69
Nocturnal pain	59
Hunger pain	45

\* This includes 420 successfully treated patients with ulcer who were under observation for from six to thirty-six months, but does not include 42 intractable cases in which some symptoms persisted in varying degrees for months.

given temporary or no relief of symptoms to 69. In the group of 226 patients with intractable ulcers, 137, or 60.6 per cent, were rendered free from symptoms on mucin therapy, 64, or 28.3 per cent, were partially improved and there was failure or recurrence in 25, or 11.1 per cent, shortly following temporary relief of symptoms. Correction of the total of 226 by the exclusion of 9 in whom complications or failure to continue with mucin therapy for an adequate period precluded the possibility of obtaining symptomatic relief would leave a total of 217 patients, 137, or 63.1 per cent, were relieved of all symptoms, 64, or 29.4 per cent, were partially improved, and 16, or 7.5 per cent, failed to obtain relief. The most significant results were obtained in the patients who had had a previous gastro-enterostomy, and who presented symptoms suggestive of an ulceration at the gastro-enterostomy stoma or of an exacerbation of the original lesion. The failure of the customary orthodox medical management to relieve this type of patient is so well known that additional surgical therapy is usually urged in order to prevent an extension of the existing pathologic condition. In 56 patients with a recurrence of symptoms after



TABLE 3—*Report Showing Recurrence of Symptoms in the Intractable Case of Duodenal Ulcer*

Place + or 0 in square depending on the presence or absence of symptom										Diagnosis Duodenal ulcer										Date of monthly report												
Name of Patient R H		1932 Oct		Nov		Dec		Jan 1933		Name of Physician B W S, Louisville, Ky										April		May										
Day of month		19	26	3	10	17	27	3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17	24	31	7	14	21	28	6*	13†	20
Time of mucin treatment		100 Gm daily in 12 hourly doses										100 Gm in 6 daily doses at 2 hour intervals																				
Nausea		0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	+	+	+	+	+	+	0
Vomiting		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	+	+	+	+	+	+	0
Pyrosis		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Tructation		+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Belching		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Flatulence		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Epigastric pain		+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	0	0	+	+	+	+	+	+	0
Lpigastric discomfort		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	+	+	+	+	+	+	0
Fpigastric tenderness		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	0	0	0	+	+	+	+	+	+	0
Anorexia		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Nocturnal pains		+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Hunger pangs		0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Constipation		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Diarrhea		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+	+	+	+	+	+	0
Hematemesis		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Melena (benzidine)		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastric analysis																																
Free hydrochloric acid	62																															
Total acids	72																															
Red blood count																																
Hemoglobin																																
Weight	168		175				177		180												189					183						
Belladonna dose																																

\* Roentgenogram of May 6, 1933, showed a definite penetrating duodenal ulcer

† Resection of pylorus

a gastro-enterostomy, it was possible to obtain complete control of all the subjective symptoms in 36, partial relief in 16 and no relief in 4. To this group may be added 13 additional patients who had had operations other than gastro-enterostomy, and in whom symptoms had recurred. Ten patients in this group were relieved completely by mucin therapy, 1 was partially improved and 2 failed to obtain relief.

*Failures*—There was a total of 93 failures, which included 61 patients who may be properly excluded because they either stopped the mucin therapy before its effect could be determined or persisted in other types of therapy at the same time. Some had complicating conditions such as diabetes, cholecystitis and nephrosis, all of which interfered with the main objective. The 32 unexplainable failures or recurrences after a temporary relief occurred in patients despite attention to all details of the mucin management. Recurrence of symptoms while still receiving mucin in 6 persons with intractable and in 1 person with simple ulcers and the occurrence of perforation in 1 and of acute massive hemorrhages in 4, all unexplainable, emphasize the limitations of mucin therapy (table 3).

#### COMMENT

Although something is known about the chemistry of mucin much remains to be learned. Mucin is a glucoprotein containing glucuronic acid, known to detoxicate certain substances such as phenol. The toxic substances in question combine with glucuronic acid and are eliminated in the urine as glucuronates. The question whether glucuronic acid is synthesized in the body is disputed. But obviously, if glucuronic acid is not synthesized in the body, and is used excessively for detoxifying purposes, the amount of mucin present would tend to be diminished. It is interesting to note that damage to the liver and gastroduodenal ulcer are frequently associated in the experimental animal. This important phase of mucin chemistry and metabolism is now being investigated by Miller and Crandall.<sup>7</sup>

A chemical quantitative method for following the secretion of mucin has been devised by Farmer and Anderson of the Northwestern University Medical School, and preliminary investigation has suggested a deficiency of mucin in many patients with ulcer, at least during active secretory states. Such a deficiency was observed by Hurst<sup>8</sup> in 10 per

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7 Miller, C. O., and Conner, J. A. Origin of Glucuronic Acid in Urine of Rabbits, *Proc. Soc. Exper. Biol. & Med.* **30** 630, (Feb.) 1933. Miller, C. O., Brazda, F. G., and Elliott, E. C. Studies on Metabolism of Glucuronic Acid in Dog, *ibid.* **30** 633 (Feb.) 1933. Miller, C. O., Siehrs, A. E., and Brazda, F. G. Glucuronic Acid as Growth Factor in Guinea Pigs, *ibid.* **30** 636 (Feb.) 1933. Crandall, L. A., Roberts, G. M., and Gibbs, J. W. The Beneficial Effect of Mucin and Chondroitin in Experimental Liver Damage, *ibid.* **29** 1082 (June) 1932.

8 Hurst, A. F. The Unity of Gastric Disorders, *Brit. M. J.* **2** 89, 1933.

cent of all normal young adults, who he believes are predisposed to the formation of ulcers since they have not only this deficiency of mucus but also hyperchlorhydria and short, high stomachs which empty rapidly. Feeding gastric mucin to these predisposed persons should meet this deficiency and thus serve as a prophylactic therapy against gastroduodenal ulcerative disease.

Physiologists teach that mucus has the function of protection and lubrication. That it lubricates is obvious. That it protects the stomach from autodigestion has been maintained since the time of Spallanzani. Evidence in support of this contention has been presented by Claude Bernard,<sup>9</sup> Schiff,<sup>10</sup> Klug,<sup>11</sup> and Whitlow.<sup>12</sup> Whitlow, working with Ivy, confirmed the belief that the mucin-containing cells of the gastric epithelium are the last layer of the gastric wall to be digested by gastric juice, and demonstrated that hydrochloric acid-pepsin diffuses slowly through a film of mucus, and that if the film of mucus covering the mucosa of the pyloric antrum is wiped away the application of tenth-normal hydrochloric acid causes bleeding much sooner than otherwise.

The Pavlov school has held that gastric mucus not only functions as a physical protective substance, but also neutralizes or buffers acid. There exists a conflict of opinion regarding the function of the normally secreted mucus in controlling gastric acidity. This is due to the inability to measure the output of the mucus-secreting cells of the entire stomach during digestion. Bonis<sup>13</sup> and Mitchell<sup>14</sup> found that the buffers of gastric juice are almost entirely dialyzable, indicating that the mucus itself has little buffer value. However, Mitchell observed that 100 cc. of highly buffered mucus is capable of inhibiting the proteolytic action of 40 cc. of gastric juice by a combined neutralizing, diluting and buffering action, and pointed out that this function would be of greatest value under normal conditions after the evacuation of a meal. If one leg of a pithed frog is placed in gastric juice containing a 2 per cent solution of mucin and the other leg is placed in gastric juice without mucin, the latter is digested to a far greater extent than the former.

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9 Bernard, Claude. *Leçons la physiologie et la pathologie du système nerveux*, Paris, J. B. Baillière et fils, 1856, vol. 2.

10 Schiff, J. M. *Leçons sur la physiologie de la digestion*, Paris, H. Loescher, 1867, vol. 2.

11 Klug, de F. *Pourquoi les ferments proteolytiques ne digerent-ils pas l'estomac et l'intestin sur le vivant?* *Arch. internat. de physiol.* **5**: 297, 1907.

12 Whitlow, J. E. *The Protective Action of Mucus*, master's thesis, Loyola University (unpublished).

13 Bonis, A. *Magenschleim und Saurebindung, zugleich ein Beitrag zur Titration mit Indikatoren und zur elektrometrischen Titration des Magensafts*, *Ztschr. f. klin. Med.* **113**: 611, 1930.

14 Mitchell, T. C. *Buffer Substances of Gastric Juice and Their Relation to Gastric Mucus*, *J. Physiol.* **73**: 427 (Dec.) 1931.

This shows that mucin retards, but does not entirely inhibit, the digestive action of gastric juice. With the evidence at hand it can only be stated that mucus and the mucin-containing cells of the gastric epithelium protect the mucosa from physical and chemical trauma, gastric mucus per se probably plays only a minor rôle in the control of gastric acidity during digestion, and gastric mucin inhibits the action of pepsin in gastric juice.<sup>15</sup>

The iso-electric point of gastric mucin is between  $p_{H}$  3 and 3.5, the hydrogen ion concentration at which free acid is measured (by Topfer's test) and at which mucin is least soluble, thus making it most efficient as a chemical and physical protective agent during the active secretory phases. Bucher's investigation on the "Protective Action of Gastric Mucus"<sup>16</sup> confirmed these findings and interpretations. He believed that the problem still to be solved is whether mucus exerts a protective action against the stomach's own juice, and whether a deficiency in this protective action may not be a causal factor in peptic ulcer. Leriche<sup>17</sup> estimated that there are more than 13,000,000 cells in the stomach constantly secreting mucus, which must play an important rôle in gastric physiology. His studies on the staining characteristics of mucus suggests that the fundus is better protected than the antrum by its heavy layer of mucus. He concluded that gastric mucus is of great importance in the physiology and pathology of the stomach and that "mucus of the stomach does not deserve the contempt in which it has been held up to this time."

After preliminary laboratory tests relating to the manufacture and biologic assay of the original gastric mucin, it was thought that no difficulties would be encountered in the manufacturing process. This was found not to be the case. The product varied. Since December 1931, therefore, every batch of the manufactured product has been assayed for (1) its buffer value, (2) its gastric secretagogue value, (3) the presence of irritating amines and (4) its odor and taste. In addition, aerobic and anaerobic bacteriologic counts have been made, and are being made, on the different batches. It has been found that acceptable gastric mucin compares favorably in this respect with certain powdered milks (attempts are being made to prepare a sterile product). If the batches do not meet the requirements of the Gastric Mucin Committee they are rejected.

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15 Babkin, B. P., and Komarov, S. A. The Influence of Gastric Mucus on Peptic Digestion, *Canad. M. A. J.* **27** 463, 1932.

16 Bucher, R. Nature of Protective Action of Gastric Mucus, *Deutsche Ztschr. Chir.* **236** 485, 1932.

17 Leriche, R. Necessité d'une systematique de la fonction des glandes à mucus du point de vue de la physiologie, de la pathologie et de la thérapeutique. *Presse med.* **40** 650 (April 27) 1932.

## CONCLUSIONS

1 A study based on questionnaires concerning 494 patients with peptic ulcer treated by clinicians throughout the United States has demonstrated the ability of gastric mucin to control all the symptoms in 70.5 per cent and to afford a partial relief of symptoms in 23 per cent, while failure to afford any relief occurred in 6.5 per cent

2 In 217 patients with intractable ulcers who could not be relieved of symptoms by medical management, of whom 69 had been submitted to previous surgical procedures, gastric mucin afforded complete relief in 63.1 per cent, partial relief in 29.4 per cent, and no relief in 7.5 per cent

3 The results obtained in this group of patients with intractable ulcers suggests the possibility of obtaining symptomatic relief with gastric mucin in a relatively high percentage of patients in whom accepted orthodox measures, including operation, have failed

4 The permanence of the results is not considered, owing to the limited periods of observation

# PARALYSIS OF THE BLADDER IN DIABETIC PATIENTS

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## INTRODUCTION

Too little attention was paid to neurologic complications and diseases in my group of diabetic patients until Dr Jordan joined Dr H F Root, Dr Piscilla White and me in 1930. For the next two and a half years he sought and found much which had been overlooked, disregarded or neglected. Already my associates and I feel indebted to him for his papers on cerebrovascular accidents, convulsions in diabetic patients, neurologic manifestations of hypoglycemia<sup>1</sup>—the two papers which appear in this issue of the ARCHIVES and a forthcoming paper on neuritis. We realize that much of the neurologic field in our practice has been only partially cleared, but we hope that before long the whole of it can be ploughed thoroughly. We regret that following Dr Jordan's years in Boston and later in Germany, he went to Richmond, Va., but we feel sure that he will continue his painstaking studies of diabetes.

ELLIOTT P JOSLIN

✓ Among our diabetic patients we have seen a number with paralysis of the urinary bladder. After the elimination of those cases due to recognized causes of this condition, such as senility, mechanical obstruction, syphilis, combined system disease, injuries of the spinal cord, transverse myelitis and tumor of the spinal cord, we still have several cases not easily explained. In this article we present seven such cases for consideration.

In the absence of a well recognized cause of the paralysis, one must consider the various conditions existing in each case.

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From the George F Baker Clinic of the New England Deaconess Hospital, Dr Elliott P Joslin, Medical Director.

1 Jordan, W R, and Watters, P. Spontaneous Cerebral Vascular Accidents in Diabetes, *Am J M Sc* **186** 488 (Oct) 1933. Jordan, W R. Epilepsy and Convulsions in Diabetes, *Arch Int Med* **52** 664 (Nov) 1933, Neurological Manifestations of Hypoglycemia, *New England J Med* **209** 715 (Oct 12) 1933.

All the patients were middle-aged, their ages ranging from 42 to 60 years, with an average of 51.1 years. There were four women and three men. The duration of the diabetes varied from less than one year in case 5,494 to eleven and eight-tenths years in case 9,025, with an average of six and one-tenth years at the onset of symptoms in the bladder.<sup>1</sup> The diabetes was mild in two cases, moderate in four and severe in one. The evidence indicates that a considerable period of inadequately controlled diabetes preceded the onset of the disturbance in the bladder in four cases, but not in the other three. All showed arteriosclerosis varying in degree from slight to advanced. There was no evidence that foci of infection exerted any influence on the disturbance in the bladder. Syphilis was not found in any case. Achlorhydria occurred in cases 8,404 and 3,645, in each the patient was at one time anemic. The use of alcohol as a cause of neuropathy seems remote, although two patients admitted its use to a slight degree. The spinal fluid was examined in five cases and showed no evidence of syphilis or of tumor of the spinal cord. In two specimens there was the slightest possible trace of globulin, a finding noted by Root and Rogers<sup>2</sup> in diabetic neuritis.

In the following brief histories we list neurologic observations.

#### REPORT OF CASES

CASE 1,443—A man, 44 years old, who had diabetes for seven years, suffered from urinary retention (residual urine, 2,100 cc). He complained of lancinating pains in the arms, chest and legs. Examination revealed pupils reacting less well to light than to distance, slight ataxia of the arms and legs and slight hypotonia. The knee jerks, which had been normal the year before, were absent, as were the ankle jerks. The Wassermann reactions of the blood and cerebrospinal fluid were negative. No written urologic record can be found, but the physician then in charge believes that cystoscopic examination was done and that it revealed no genito-urinary condition which might have caused the paralysis.

The patient died two and five-tenths years later of diabetes.

CASE 3,645—A man, 60 years old, with diabetes of nine years' duration and advanced arteriosclerosis, began to suffer from nocturia, dribbling and incontinence at night. He also had shooting pains in the left thigh at night and complained of cold feet at night. During this period he had difficulty controlling the anal sphincter. Examination revealed slight mental confusion, pupils sluggish to light, a slightly sluggish right knee jerk, a very sluggish left knee jerk or absence of the jerk, absence of ankle jerks, decreased sensitivity over the lower portion of the right leg and foot and loss of tone of the anal sphincter. The Wassermann reactions of the blood and spinal fluid and the colloidal gold test were negative. The patient denied the use of alcohol. Urologic examination revealed residual urine (720 cc) without prostatic or urethral obstruction. The bladder mucosa showed mild cystitis. Trabeculation was moderate. There was no diverticulum.

1a It is possible that the initial symptoms in case 5,494 were due merely to glycosuria and that the real disturbance in the bladder began seven years later.

2 Root, H. F., and Rogers, M. Diabetic Neuritis with Paralysis, New England J. Med. **202** 1049, 1930.

When the patient was first seen in September, he showed no evidence of anemia. The red blood cell count was 4,960,000, and the hemoglobin content was 91 per cent (Sahli). On January 27, following an attack of grip, he returned to the hospital. At this time there was definite, though not marked, hypochromic anemia. The total gastric acidity was 30 cc of sodium hydroxide, but there was absence of lactic acid and free hydrochloric acid. The size of the red blood cells was below the average normal. During the next month pills of ferrous carbonate 45 grains (27 Gm) daily, were given, and during the second month in the hospital twelve intramuscular injections of liver extract were given. From then until May 15 three or four intramuscular injections of liver extract were given. The red blood cell count on March 20 was 3,650,000 (260,000 less than in January), but on May 15 the count was 5,660,000 and the hemoglobin content, 80 per cent. A diagnosis of secondary anemia was made, but the anemia may have been primary, the manifestations being precipitated and altered by infections. The retarded response to liver therapy may have been due to burns on the feet during the early part of the therapy. He survived amputation of a leg for gangrene in April 1934.

CASE 4,023—A woman, 60 years old, with diabetes of three years' duration and moderate arteriosclerosis, complained of pain in the right leg on walking. Paresthesia disturbed her at night. Examination revealed a distended bladder (residual urine, 2,580 cc). The pelvic and neurologic examinations gave negative results. The Wassermann reactions of the blood and spinal fluid were normal. Dr. James B. Ayer found no evidence of a nondiabetic lesion in the spinal cord. Cystoscopy revealed general redness of the bladder mucosa, with an abnormal amount of trabeculation.

The patient was in a satisfactory condition in April 1934, eight years after the onset, but she still required periodic catheterization and had residual urine at times as high as 2,730 cc.

CASE 5,494—A man, 47 years old, noticed involuntary urination at night at the onset of diabetes. Five years later he began to have paresthesia of the legs and subsequently pains in the legs. Two years later the bladder was found to be distended (residual urine, 360 cc). Examination revealed moderate arteriosclerosis, normal pupils and cranial nerves, sluggish knee and ankle jerks, weakness and atrophy and fibrillary twitchings of the muscles of the legs and, to a less degree, of the arms and variable sensitivity of the skin with areas of both hypo-esthesia and hyperesthesia. The Wassermann reaction of the blood was negative, and the spinal fluid was normal except for the slightest possible trace of globulin. No history of use of alcohol was obtained. Urologic examination revealed a slight irregularity of the prostate, but it was insufficient to cause obstruction. Trabeculation of the bladder was moderate.

He died seven months later of a gas bacillus infection following appendectomy.

CASE 6,360—A woman, 55 years old, with diabetes of seven years' duration and mild arteriosclerosis, was found to have a distended bladder (residual urine, 900 cc). She had no other neurologic symptoms. Examination revealed absence of the ankle jerks but no other neurologic signs. The Wassermann reaction of the blood was negative. There was no history of the use of alcohol. Cystoscopic examination revealed moderate chronic inflammation of the bladder. No cause other than neurologic disturbance was found.

The patient was alive more than six years after the onset of paralysis, although she had suffered amputation of a leg for gangrene and had a thyroidectomy. The



report of the last nurse indicates residual urine of 270 cc. In April 1934 a roentgenogram revealed a condition of the spine similar to that in two cases of spontaneous fracture recently reported by Root, White and Marble<sup>3</sup>

CASE 8,404—A woman, 42 years old, with diabetes of four and eight-tenths years' duration and slight arteriosclerosis, had diarrhea for six months and finally hematuria. Examination revealed no neurologic signs except sluggish knee jerks and absence of the ankle jerks. The bladder was distended (residual urine, from 360 to 900 cc), and considerable gas was present. From rough tests the gas was thought to be air which presumably entered the bladder during catheterization. There was no history of the use of alcohol. No cause for the diarrhea was found except achlorhydria and a weak anal sphincter. The Wassermann reaction of the blood was negative, as was the spinal fluid except for the slightest possible trace of globulin. Cystoscopic examination revealed marked chronic cystitis with a number of hemorrhagic spots in the wall of the bladder. No tumor or diverticulum was present. The appearance was consistent with a neurologic cause. Roentgenograms of the urinary tract showed no abnormality other than air in the bladder.

Gastric analysis revealed an absence of free hydrochloric acid. Two years previously the red blood cells numbered 3,350,000, and liver therapy was recommended. At the time of our examination she was not anemic, but the possibility of pernicious anemia was considered. She died four months later of pneumonia.

CASE 9,025—A woman, 50 years old, with mild diabetes of eleven and eight-tenths years' duration, a blood pressure of 200 systolic and 120 diastolic and moderate arteriosclerosis, entered the hospital because of urinary retention and uremia. At first the retention was thought to be due solely to a urethral stricture, but correction of this defect, while causing some amelioration of the symptoms, did not abolish the retention, which seemed to be due to paralysis of the wall of the bladder. There were no neuritic symptoms. Examination revealed normal pupils. The knee reflexes were present. The Wassermann reaction of the blood was negative. Cystoscopic examination was not done at first for fear of hemorrhage if the bladder was emptied. Later the amount of residual urine varied from 90 to 300 cc. For the last three years the urethra has maintained a normal caliber of a no. 22 French catheter, yet the residual urine has persisted, and the nonprotein nitrogen content of the blood has varied from 44 to 62 mg. since June 1932.

She was living in March 1934, nearly four years after the onset.

#### COMMENT

Study of these cases reveals no definite cause of the paralysis. In six the symptoms in the bladder accompanied paresthesia and changes in the reflexes attributable to neuritis of diabetic origin. Two patients had achlorhydria and at one time had anemia, though not definitely of the pernicious type. Arteriosclerosis and diabetes were the only diseases present in all cases. The former may give rise to paralysis, and we believe that it was a factor in these cases. The relationship between arteriosclerosis and diabetic neuropathy was described recently by Woltman and Wilder.<sup>4</sup> The influence of diabetes on paralysis of the bladder

3 Root, H. F., White, P., and Marble, A. Abnormalities of Calcium Deposition in Diabetes Mellitus, *Arch Int Med* **53** 46 (Jan.) 1934.

4 Woltman, H. W., and Wilder, R. M. Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch Int Med* **44** 576 (Oct.) 1929.

may be judged in part by its influence on the nerve tissue elsewhere in the body. That diabetes is often associated with neuropathy is well known. Such neuropathy is frequently designated neuritis and in some cases as diabetic tabes. Granting that neuritis was present in these cases, are we justified in suspecting it of causing the vesical paralysis?

#### PARALYSIS OF THE BLADDER AND NEURITIS

Involvement of the bladder in neuritis of any etiology appears to be rare. Yet many authors have reported evidence of involvement of the spinal cord in various forms of neuritis, and Campbell<sup>5</sup> stated that "in posterior tract disease, bladder disturbances are likely to be the rule." Feiling<sup>6</sup> stated that the central as well as the peripheral nervous system is damaged in many cases of neuritis. Hyslop and Kraus<sup>7</sup> reviewed the literature on lead paralysis and concluded that the neuritis involves the cord as well as other parts of the nervous system. Eijkman<sup>8</sup> found changes in the spinal cord in experimental beriberi, and Voegthin and Lake<sup>9</sup> reported changes in the spinal cord in a similar deficiency neuritis in a large proportion of their animals. Boxwell<sup>10</sup> reported vesical involvement in alcoholic neuritis, Campbell<sup>5</sup> in alcoholic, lead and toxic neuritis and Caulk and Greditzer<sup>11</sup> in lead poisoning. Holmes<sup>12</sup> found involvement of the sphincters in cases of polyneuritis of the type with facial diplegia, and Harris<sup>13</sup> said that paralysis of the sphincter is occasionally seen in neuritis. Kennedy<sup>14</sup> mentioned paralysis of the sphincter in diphtheritic neuritis.

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5 Campbell, M. F. Bladder Disturbances of Nerve Lesion Origin, *M. J. & Rec. (supp.)* **119** 40 (March 5) 1924.

6 Feiling, A. Multiple Neuritis, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1921, vol. 6, p. 647, quoted by Hyslop and Kraus<sup>7</sup>.

7 Hyslop, G. H., and Kraus, W. M. Pathology of Motor Paralysis by Lead, *Arch. Neurol. & Psychiat.* **10** 444 (Oct.) 1923.

8 Eijkman, C. Eine Beri-Beri-ähnliche Krankheit der Hühner, *Virchows Arch. f. path. Anat.* **148** 523, 1897.

9 Voegthin, C., and Lake, G. C. Experimental Mammalian Polyneuritis Produced by a Deficient Diet, *Am. J. Physiol.* **47** 558, 1919.

10 Boxwell. Disordered Bladder Function in Nervous Diseases, *Tr. Roy. Acad. Med. Ireland* **32** 63, 1914.

11 Caulk, J. R., and Greditzer, H. G. Bladder in Diseases of Central Nervous System, *Am. J. Syph.* **1** 42, 1917, *Interstate M. J.* **23** 36, 1916.

12 Holmes, G. *Brit. M. J.* **2** 37, 1917, quoted by Wilson, G., and Robertson, H. F. Facial Diplegia in Polyneuritis, *Am. J. M. Sc.* **183** 680, 1932.

13 Harris, W. Multiple Peripheral Neuritis, *Proc. Roy. Soc. Med. (Sect. Neurol.)* **16** 13, 1923.

14 Kennedy, F. Focal Infections Implicating the Nervous System, *Am. J. M. Sc.* **185** 305, 1933.

## DISTURBANCES IN THE BLADDER IN DIABETES DUE TO INVOLVEMENT OF THE SPINAL CORD

Reports dealing with vesical paralysis in persons with diabetes are rare. Marchal de Calvi<sup>15</sup> quoted LeBret as reporting a diabetic patient with a slight disturbance in the bladder, but he did not disclose the nature of the change. Bonardi<sup>16</sup> reported a diabetic patient with loss of sphincter control. Root<sup>17</sup> mentioned two diabetic patients with concomitant pernicious anemia in whom there developed paralysis of the bladder. Von Noorden and Isaac<sup>18</sup> referred to urinary urgency, especially at night, not apparently due to the polyuria in persons with diabetes. Joslin<sup>19</sup> reported cases of diabetes of this series (cases 1,443 and 5,494) as illustrations of pseudotabes, but did not mention the symptoms in the bladder. McKittrick and Root<sup>20</sup> added a third case. On the other hand, Caulk and Greditzer<sup>11</sup> reported one hundred and seventeen cases of disturbance in the bladder due to involvement of the spinal cord without mentioning diabetes as a cause in any case. Williamson<sup>21</sup> and Smith<sup>22</sup> denied that changes in the sphincter are caused by diabetes. Yet clinical or pathologic evidence of involvement of the spinal cord in diabetic patients has often been reported<sup>23</sup>. One form

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15 Marchal de Calvi. *Recherches sur les accidents diabetiques*, Paris, P Asselin, 1864

16 Bonardi, E. *Sclerosi diffusa pseudo-sistematizzata della midolla spinale con polinevrite in un caso di diabete mellito*. Morgagni **39** 557, 1897

17 Root, H F. *New Cases of Diabetes and Pernicious Anemia*, New England J Med **208** 819, 1933

18 von Noorden, C, and Isaac, S. *Die Zuckerkrankheit und ihre Behandlung*, Berlin, Julius Springer, 1927

19 Joslin, E P. *Treatment of Diabetes Mellitus*, ed 4, Philadelphia, Lea & Febiger, 1928, p 734

20 McKittrick, L S, and Root, H F. *Diabetic Surgery*, Philadelphia, Lea & Febiger, 1928, p 253

21 Williamson, R T. *Symptoms Due to Peripheral Neuritis or Spinal Cord Lesions in Diabetes Mellitus*, Rev Neurol & Psychiat **5** 550, 1907

22 Smith, W A. *Diabetic Neuritis*, South M J **19** 773, 1926

23 Pryce, T D. *Perforating Ulcers of Both Feet Associated with Diabetes and Ataxic Symptoms*, Lancet **2** 11, 1887. Pavy. *On Diabetes*, M News **51** 357 (Sept 24) 1887, quoted by Pryce<sup>22</sup>. Leyden, E. *Die Entzündung der peripheren Nerven*, Deutsche mil-arztl Ztschr **17** 49 and 100, 1888, quoted by Althaus. Althaus, J. *Neuritis of the Circumflex Nerve in Diabetes*, Lancet **1** 455, 1890. Minor, L. *Etude de l'etiologie du tabes*, Arch de neurol **17** 362, 1889. Sandmeyer, W. *Beitrag zur pathologischen Anatomie des Diabetes mellitus*, Deutsches Arch f klin Med **50** 381, 1892. Leichtentritt, H. *Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus*, Berlin, G Schade, 1893, p 32, quoted by Woltman and Wilder<sup>4</sup>. Leyden. *Beitrage zur Klinik des Diabetes mellitus*, Wien med Wchnschr **43** 926, 1893. Williamson, R T. *Changes in the Posterior Columns of the Spinal Cord in Diabetes Mellitus*, Brit M J **1** 398, 1894, *Changes in the Spinal Cord in Diabetes Mellitus*, *ibid*

of diabetic neuritis is even spoken of as pseudotabetic.<sup>24</sup> Nicolesco and Raileanu<sup>25</sup> noted that the extrapyramidal and central vegetative systems were particularly damaged in diabetes. In this clinic we have noted Argyll Robertson pupils, ataxia and loss of sense of position of the big toe, apparently due to diabetes. Furthermore, diabetes is a disease of elderly people, and it is usually associated with considerable arteriosclerosis which also causes involvement of the spinal cord (Woltman,<sup>26</sup> Price<sup>27</sup>). This evidence of potential involvement of the bladder in diabetes gives ground for suspecting diabetic neuropathy as a cause of the paralysis.

In spite of eliminating cases of combined system disease, we are confronted with the possibility of this disease as a cause, since a study of the history in one case and of the subsequent course in another disclosed anemia. All seven in the series may represent cases of combined system disease with latent anemia, but the available data (absence of anemia in five cases and dissimilarity between the changes in the nerves and those usually found in combined system disease) do not make this supposition reasonable.

The mechanism of the production of the paralysis is not known. Elliott<sup>28</sup> showed the tonic action of the central nervous system on the bladder, and we have mentioned many authors who found lesions of the spinal cord, frequently in the posterior tract, in diabetic patients. Pre-

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1 122, 1904. Nonne, M. Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lahmung bei Diabetes mellitus, Berl klin Wchnschr **33** 207, 1896. Souques, A., and Marinesco, G. Lesions de la moelle epiniere dans un cas de diabete sucre, Rev neurol **5** 242, 1897. Marinesco, G. Cas de paraplegie diabetique, *ibid* **9** 719, 1901. Ossokine, N. Contribution a l'etude de l'anatomie pathologique de la moelle dans le diabete sucre, Kazanskiy med j **1** 370, 1901, abstr, *ibid* **10** 993, 1902. Schweiger, L. Ueber die tabiformen Veranderungen der Hinterstrange bei Diabetes, Wien med Wchnschr **57** 1549, 1907. Bonardi.<sup>16</sup> Woltman and Wilder.<sup>4</sup>

24 Major, R. H. Tabes Diabetica, J A M A **83** 2004 (Dec 20) 1924. Wakefield, E. G. Diabetic Neuritis, Proc Staff Meet, Mayo Clin **3** 256, 1928. Angle, F. E. Tabes Diabetica, U S Nav M Bull **26** 81, 1928. (The patient with pseudotabetic diabetes whose case was reported by Angle had symptoms in the bladder, but he also had an enlarged prostate and uncontrolled diabetes, which may give rise to severe symptoms, which are probably brought about by local prostatic irritation and disappear when the diabetes is regulated. The cases we report here are not of this type.)

25 Nicolesco, I., and Raileanu, D. Alterations du systeme nerveux central dans deux cas de diabete sucre, Compt rend Soc de biol **95** 122, 1926.

26 Woltman, H. W. Arteriosclerosis of the Nervous System, M Clin North America **5** 511, 1921.

27 Price, G. E. Arteriosclerosis of the Nervous System, M J & Rec **118** 425, 1923.

28 Elliott, T. R. Innervation of the Bladder and Urethra, J Physiol **35** 367, 1907.

sumably, diabetes affects the nerves to the bladder as it does those to the legs, either directly or indirectly through the lesions of the spinal cord. Woltman and Wilder<sup>4</sup> described these lesions and summed up the literature on the subject.

#### TREATMENT

The objectives are to maintain proper control of the diabetes, to administer a properly balanced diet containing an abundance of vitamins and to keep the patient in as good general condition as possible. The local treatment is directed against urinary retention and infection. Prolonged constant drainage has been helpful. Periodic catheterization has been the rule. Various authors<sup>29</sup> have described forms of treatment for the bladder affected by changes in the spinal cord. Cahill<sup>29d</sup> and Priestley<sup>30</sup> recommended systematic pressure on the bladder to stimulate the automatic emptying noted by Elliott<sup>28</sup> and Osgood<sup>31</sup>. We have used this method in only one case (case 4,032) and without success, although it would seem especially adaptable to diabetic patients, since we have not infrequently noted a return of the reflexes in patients with diabetic neuritis and almost all patients with paralysis of skeletal muscles eventually regain control of the muscles. Resection of the presacral (sympathetic) nerve, as practiced in some cases by Learmouth,<sup>29f</sup> has not been tried, because in diabetes there is a more or less generalized involvement of the nervous system and not a sharp localization to one set of nerves such as the parasympathetic system. Goldberg,<sup>32</sup> in discussing retention due to urethral stricture, recommended that diabetic patients with marked strangury, especially at night, be catheterized, so that retention of urine, curable in the beginning, will not be overlooked. In our case 9,025, with urethral stricture, we were unable to avoid the subsequent retention, even though catheterization and dilation of the stricture were repeatedly done. The subsequent retention seemed due to paralysis of the wall of the bladder, but it may have

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29 (a) Smith, G. Bladder Disturbance Due to Nerve Lesions, *J A M A* **69** 1323 (Oct 20) 1917. (b) Burns, J E. Bladder Changes Due to Lesions of the Central Nervous System, *Surg, Gynec & Obst* **24** 659, 1917. (c) Corbus, B C, and O'Connor, V J. The Tabetic Bladder from the Standpoint of the Urologist, *J A M A* **79** 1750 (Nov 28) 1922. (d) Cahill, G F. Treatment of Bladder Paralysis Due to Nontabetic Spinal Cord Lesions, *Am J Surg* **5** 442, 1928. (e) Boyd, M L, and Bailey, M K. Suprapubic Cystotomy in Bladder Paralysis, *J Urol* **21** 623, 1929. (f) Learmouth, J R. Neurosurgery in Treatment of Diseases of Urinary Bladder, *J Urol* **26** 229, 1931. (g) Caulk and Greditzer<sup>11</sup>. Campbell<sup>5</sup>.

30 Priestley, J T. Spinal Cord Bladder, *J Urol* **21** 635, 1929.

31 Osgood, A T. Significance of Disturbances of the Function of the Bladder, *Bull New York Acad Med* **2** 194, 1926.

32 Goldberg. Retention of Urine Due to Complications of Urethral Stricture, *Ztschr f Urol* **19** 359, 1925.

been contributed to by the previous stricture. We believe that diabetic patients are particularly susceptible to neuritis and that a factor insufficient to produce neuritis in a person who has no diabetes may cause it in a person with diabetes.

#### SUMMARY AND CONCLUSIONS

1 Seven cases of diabetes with urinary retention are reported.

2 The nature of the disturbance in the bladder, the absence of any other known cause and in many cases the close association with diabetic neuritis suggest that the changes in the bladder are due to such neuropathy.

3 The treatment consists of treatment of the diabetes and of any associated neuritis, the prevention or treatment of urinary infection and catheterization at intervals to prevent uremia.

4 The prognosis is not good. Three of the seven patients are dead. None of our patients has regained the power to empty the bladder completely. The blood nitrogen, on the other hand, has not risen to a serious level, and the general health of the patients has remained reasonably good.

# NEUROPATHY IN DIABETES MELLITUS

LIPID CONSTITUENTS OF THE NERVES CORRELATED  
WITH THE CLINICAL DATA

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The frequent occurrence of neurologic symptoms and signs is one of the striking features noted in a clinic for the treatment of diabetes. Although the frequency of individual symptoms and signs varies, it is safe to say that about 50 per cent of diabetic patients show evidence of a disturbed nervous system. In 1884, Bouchard<sup>1</sup> noted absence of knee jerks in 28.8 per cent of diabetic patients, and in 1931 Sevringhaus<sup>2</sup> recorded pain in 49 per cent and reduced reflexes in 57.3 per cent of diabetic patients specially examined for these changes. Among 461 of our diabetic patients in whom the patellar and achilles reflexes were tested, we found decreased or absent reflexes in 45.3 per cent.

Diabetic neuritis is not a new condition, yet little progress seems to have been made in its prevention or cure. Although previous to 1864 symptoms suggestive of the degeneration of nerves in diabetic persons had been reported, it was in that year that Marchal de Calvi<sup>3</sup> introduced the conception that such lesions may well be a result of diabetes. Following the publication of Bouchard's paper, many contributions to the subject were made, and in 1890 Auché<sup>4</sup> summed up the pertinent work, giving a fairly complete picture of diabetic neuritis. Since then numer-

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1 Bouchard. Sur la perte des réflexes tendineux dans le diabète sucré, *Progres med* **12** 819, 1884.

2 Sevringhaus, E. L. Study of Five Hundred Diabetics, *Am J M Sc* **182** 311, 1931.

3 Marchal de Calvi. Recherches sur les accidents diabetiques, Paris, P. Asselin, 1864.

4 Auché, B. Des alterations des nerfs peripheriques chez les diabetiques, *Arch de med exper et d'anat path* **2** 635, 1890.

ous papers have been published. Williamson<sup>5</sup> wrote profusely on the subject, and he and many others<sup>6</sup> described pathologic changes associ-

5 Williamson, R. T. Changes in the Posterior Column of the Spinal Cord in Diabetes Mellitus, *Brit M J* **1** 398, 1894, On the Knee-Jerks in Diabetes Mellitus, *Lancet* **2** 138, 1897, Note on the Tendo-Achilles Jerk and Other Reflexes in Diabetes Mellitus, *Rev Neurol & Psychiat* **1** 667, 1903, Changes in the Spinal Cord in Diabetes Mellitus, *Brit M J* **1** 122, 1904, Symptoms Due to Peripheral Neuritis or Spinal Lesions in Diabetes Mellitus, *Rev Neurol & Psychiat* **5** 550, 1907, Diabetic Neuritis, *Practitioner* **112** 85 (Feb.) 1924

6 (a) Minor, L. Etude de l'étiologie du tabes, *Arch de neurol* **17** 362, 1889 (b) Pryce, T. D. Perforating Ulcers of Both Feet Associated with Diabetes and Ataxic Symptoms, *Lancet* **2** 11, 1887, (c) Diabetic Neuritis with a Clinical and Pathological Description of Three Cases of Diabetic Pseudotabes, *Bram* **16** 416, 1893 (d) Eichhorst, H. Neuritis diabetica und ihre Beziehungen zum fehlenden Patellarsehnenreflex, *Virchows Arch f path Anat* **127** 1, 1892 (e) Sandmeyer, W. Beitrag zur pathologischen Anatomie des Diabetes mellitus, *Deutsches Arch f klin Med* **50** 381, 1892 (f) Leyden. Beiträge zur Klinik des Diabetes mellitus, *Wien med Wchnschr* **43** 926, 1893 (g) Leichtentritt, H. Ein Beitrag zur Erkrankung peripherer Nerven und des Rückenmarks bei Diabetes mellitus, Berlin, G. Schade, 1893, p. 32, quoted by Woltman and Wilder<sup>6a</sup> (h) Fraser, T. R., and Bruce, A. Case of Diabetic Neuritis, *Edinburgh M J* **42** 300, 1896, Multiple Diabetic Neuritis, *Brit M J* **1** 1149, 1895 (i) Nonne, M. Ueber Poliomyelitis anterior chronica als Ursache einer chronisch progressiven atrophischen Lahmung bei Diabetes mellitus, *Berl klin Wchnschr* **10** 207, 1896 (j) Fleming, R. A. Two Cases of Peripheral Neuritis *Bram* **20** 56, 1897 (k) Souques, A., and Marinesco, G. Lesions de la moelle epiniere dans un cas de diabete sucre, *Rev neurol* **5** 242, 1897 (l) Bonardi, E. Sclerosi diffusa pseudo-sistemizzata della midolla spinale con polinevrite in un caso di diabete mellito, *Morgagni* **39** 557, 1897 (m) Leyden and Goldscheider. Die Erkrankungen des Rückenmarks und der Medulla oblongata, in Nothnagel, H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1900, vol. 10, p. 500, quoted by Woltman and Wilder<sup>6a</sup> (n) Naunyn, B. Der Diabetes mellitus, in Nothnagel, H. *Specielle Pathologie und Therapie*, Vienna, A. Holder, 1900, vol. 7, p. 251, quoted by Woltman and Wilder<sup>6a</sup> (o) Findlay, J. W. Changes in the Peripheral Nerves in a Case of Diabetes Mellitus, *Tr Med-Chir Soc Glasgow* **3** 441, 1902 (p) Ossokine, N. Contribution a l'etude de l'anatomie pathologique de la moelle dans le diabete sucre, *Rev neurol* **10** 993, 1902 (q) Marinesco, G. Cas de paraplégie diabetique, *ibid* **9** 719, 1901 (r) Wittmaack, K. Degenerative Neuritis bei Diabetes mellitus, *Ztschr f Ohrenh* **53** 19, 1907 (s) Schweiger, L. Ueber die tabiformen Veränderungen der Hinterstränge bei Diabetes, *Wien med Wchnschr* **57** 1549, 1907 (t) Bramwell, B. Diabetes. Marked Changes in the Posterior Tibial and Plantar Nerves, *Clin Studies* **5** 279, 1907 (u) Nicolesco, I., and Raileanu, D. Alterations du système nerveux central dans deux cas de diabete sucre, *Compt rend Soc de biol* **95** 122, 1926, (v) Lesions du système nerveux central dans le diabete sucre, *Rev neurol* **1** 31, 1927 (w) Wohl, M. G. Avitaminosis in the Course of Diabetes, *J A M A* **87** 901 (Sept 18) 1926 (x) Woltman, H. W., and Wilder, R. M. Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch Int Med* **44** 576 (Oct.) 1929 (y) Root, H. F., and Rogers, M. H. Diabetic Neuritis with Paralysis, *New England J Med* **202** 1049, 1930 (z) Auché<sup>4</sup>



ated with diabetic neuritis. Lesions have been described in the brain, spinal cord, posterior nerve roots and peripheral nerves. Auché<sup>4</sup> believed that the nerve lesions could not be explained by changes in the spinal cord, because normal nerve tissue was found proximal to a diseased portion and the peripheral part of the nerve showed greater pathologic change than the proximal portion. Woltman and Wilder<sup>6a</sup> subscribed to this view. One notes in the description of changes in the nerves the marked degeneration of myelin, which is not, however, peculiar to diabetes.

There are numerous suggestions that this degeneration of diabetic nerves may be of metabolic origin. Raven<sup>7</sup> noted the return of the knee jerks in a diabetic patient who simultaneously regained health and strength. Althaus<sup>8</sup> reported an increase in the nervous condition when the diabetic diet was limited too much, and he believed cachexia to be a cause of the neuritis. Pryce<sup>6c</sup> also suggested prolonged malnutrition as a cause, whereas Harris,<sup>9</sup> while excluding hyperglycemia and acetone bodies as causes, suggested that the cause was a neurotoxin of the autotoxemic deficiency type. Nicolesco and Raileanu<sup>6i</sup> also held to the theory of prolonged intoxication due to metabolites. Angle<sup>10</sup> reported an interesting case of diabetic tabes which developed while the urine was sugar-free, improving markedly when a diet moderately high in carbohydrate was substituted for the previous diet high in fat. Woltman and Wilder<sup>6x</sup> also noted improvement in the reflex activity when emaciated diabetic patients became properly nourished. The isolated reports of disease caused by dietary deficiency in diabetic patients, for instance, those of Wohl<sup>6w</sup> and Bitzer,<sup>11</sup> bring up the possibility of some similar condition as the cause of the changes in the nerves. Possibly on account of the well known deficiency diseases, such as combined system disease and beriberi, one notices a trend toward the belief that various forms of neuritis may be due to some dietary deficiency (Wechsler<sup>12</sup>). Why the myelin so often bears the brunt of the attack is unknown. The observation of Moore, Brodie and Hope<sup>13</sup> that in

7 Raven, T. F. Disappearance and Return of Knee-Jerks in Diabetes, *Brit M J* **1** 303, 1887

8 Althaus, J. Neuritis of the Circumflex Nerve in Diabetes, *Lancet* **1** 455, 1890

9 Harris, W. Toxic Polyneuritis, *Brain* **45** 415, 1922, Multiple Peripheral Neuritis, *Lancet* **2** 849, 1922, Multiple Peripheral Neuritis, *Proc Roy Soc Med (Sect Neurol)* **16** 13, 1923

10 Angle, F. E. Tabes Diabetica, *U S Nav M Bull* **26** 81, 1928

11 Bitzer, E. W. A Case of Beri-Beri in a Diabetic, *J Florida M A* **17** 577, 1931

12 Wechsler, I. S. Unrecognized Cases of Deficiency Polyneuritis, *M J & Rec* **131** 441, 1930

13 Moore, C. U., Brodie, J. L., and Hope, R. B. Some Effects of Inadequate Maternal Diets, *Am J Physiol* **82** 350, 1927

then experiments on the neuritis secondary to vitamin B deficiency the clinical manifestations of neuritis appeared in the young rats "only when the myelin normally should be fully laid down" is interesting and may explain why diabetic children suffer so little from neuritis. The work of Brickner,<sup>14</sup> Cherry and Crandall,<sup>15</sup> and Weil and Crandall<sup>16</sup> suggests the possibility of some lipolytic enzyme as an etiologic agent. The common observation in clinics for the treatment of diabetes that degeneration of nerves occurs far more often in the elderly person with a mild case of diabetes than in the young person with a severe case is better evidence than the experiments of Auché<sup>4</sup> and Eichhorst<sup>6a</sup> that diabetic neuritis is not a result of hyperglycemia only. One must look for a more subtle cause. Many observations incline one to admit that vascular disease is a more important factor. Pryce,<sup>6c</sup> Rimbaud<sup>17</sup> and recently Woltman and Wilder<sup>6x</sup> have all been struck by this feature and many authors<sup>18</sup> have discussed the relationship of arteriosclerosis to neuritis in persons not having diabetes. The arteriosclerosis in persons with diabetes has often been attributed to faulty fat metabolism, and it is not impossible that the degenerative changes in the nerves may be due as much to defective metabolism as to the vascular disease associated with it. Considering the definite disorder of fat metabolism in diabetes and the abnormality of the lipid myelin sheath in this disease, we wondered about the fatty substances present in the nerves of diabetic persons and the changes wrought by the diabetes.

From the earliest work on degenerative diseases of the nervous system chemical evidence of the breakdown of nervous tissue was obtained by discovery of certain products of disintegration in the cerebrospinal fluid and in the blood. The determination of phosphorus

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14 Brickner, R. M. *New York State J. Med.* **31** 885 (July 15) 1931, quoted by Weil and Crandall<sup>16</sup>

15 Cherry, I. S., and Crandall, L. A. Specificity of Pancreatic Lipase, *Am. J. Physiol.* **100** 266, 1932

16 Weil, A., and Crandall, A. L. Relationship Between Lipase and Neurotoxic Action of Dog's Serum After Experimental Liver Damage, *Proc. Soc. Exper. Biol. & Med.* **29** 388, 1932

17 Rimbaud, L. Un cas de nevríte diabétique, *Gaz. d. hôp.* **82** 1555, 1909

18 Schlesinger, H. Ueber eine durch Gefässerkrankungen bedingte Form der Neuritis, *Neurol. Centralbl.* **14** 578, 1895. Franceschi, F. Polinevrite ed arteriosclerosi del sistema nervoso centrale e periferico, *Riv. di pat. nerv.* **8** 193, 1903. Woltman, H. W. Arteriosclerosis of the Nervous System, *M. Clin. North America* **5** 511, 1921. Price, G. E. Arteriosclerosis of the Nervous System, *M. J. & Rec.* **118** 425, 1923. Alpers, B. J., and Wolman, I. J. Arteriosclerotic Disease of the Optic Nerve, *Arch. Ophth.* **6** 21 (July) 1931. Priestley, J. B. Histopathology of Peripheral Nerves Removed from Extremities Amputated for Arteriosclerotic Gangrene, *Proc. Staff Meet., Mayo Clin.* **6** 517, 1931

constitutes one of the earliest attempts to study changes under pathologic conditions Halliburton<sup>19</sup> studied phospholipid degeneration in nerve tissue and supported the theory that the phosphorus portion of the molecules was liberated, leaving behind the fatty portion of the compound The phosphorus content decreased in the tissues and increased in the blood, and the nitrogen level increased in the blood of experimental animals in which the nerve had been cut and allowed to degenerate

A few studies have been made comparing the chemical content of normal brains and brains in which a pathologic change has occurred In dementia praecox, Koch<sup>20</sup> and Koch and Mann<sup>21</sup> found that neutral sulphur was diminished while inorganic sulphur was increased The phosphorus content did not show a notable change, either as a whole or distributed

Smith and Mair<sup>22</sup> found in hemiplegic softening of the brain that the cholesterol content was increased, the excess appearing in the form of esters, while the level of cerebrosides and lipid phosphorus was reduced In dementia paralytica these authors noted that the cholesterol level was normal, while the cerebroside content was reduced 50 per cent and the lipid phosphorus balance was reduced, but to a less extent

In progressive paralysis Carbone and Pighini,<sup>23</sup> Pighini<sup>24</sup> and Pighini and Barbieri<sup>25</sup> stated that there was an increase in water, protein and cholesterol and a decrease in saturated and unsaturated phospholipids and cerebrosides They observed an increase in lipid granules when the metabolism of the cell was changed in some way, as in senescence, in poisoning or in certain diseases of the nervous system The chemical picture of paralysis is similar to that of lipid degeneration

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19 Halliburton, W D Die Biochemie der peripheren Nerven, *Ergebn d Physiol* **4** 23, 1905

20 Koch, W Zur Kenntnis der Schwefelverbindungen des Nervensystems, *Ztschr f physiol Chem* **53** 496, 1907

21 Koch, W, and Mann, S A A Chemical Study of the Brain in Healthy and Diseased Conditions, with Special Reference to Dementia Praecox, *Arch Neurol & Psychiat* **4** 174, 1909

22 Smith, J L, and Mair, W On a Method of Quantitative Analysis of Tissue Lipoids, with a Preliminary Note on Degeneration in the Brain, *J Path & Bact* **16** 131, 1911

23 Carbone, D, and Pighini, G Beitrag zur chemischen Zusammensetzung des Gehirns bei der progressiven Paralyse, *Biochem Ztschr* **46** 450, 1912

24 Pighini, G Beitrag zur chemischen Zusammensetzung des Gehirns bei der progressiven Paralyse, *Biochem Ztschr* **63** 304, 1914

25 Pighini, G, and Barbieri, P Chemische und histochemische Untersuchungen über die lipoiden Abbaustoffe des Gehirns bei der progressiven Paralyse, *Ztschr f d ges Neurol u Psychiat* **25** 353, 1914

Koch <sup>26</sup> found in the brain of a patient with dementia paralytica a slight increase in the water content in the fresh tissue, a relative increase in the protein and possibly also the cholesterol content and a decrease of lipids as a whole. Of the lipids, the unsaturated phospholipids showed the most consistent decrease, while the saturated cerebiosides and sulphatides showed less consistent decreases. He found marked increases in extractives (water-soluble substances). The lipid nitrogen and lipid phosphorus levels were decreased, while the extractive phosphorus and nitrogen values were increased. He suggested that the less stable unsaturated phospholipids break down from their physical or physicochemical combination with proteins and other lipids, with the subsequent appearance of the split products in the extractive fraction.

Singer <sup>27</sup> studied the brains of five persons with progressive paralysis and found the petroleum ether extracts increased per gram of substance. The nitrogen content expressed in per cent of dry substance, diminished. The choline nitrogen fraction, corresponding to the lecithin, was reduced to one third of normal, and in some cases there was a reduction in ammonium nitrogen also. Galactoside nitrogen could be demonstrated only in traces. The total choline-nitrogen fraction changed from the normal value of 14.1 to 3.1. He thought that the diminution of lecithin should be considered a symptom of marasmus in general rather than a specific symptom of paralysis, since it is found in cachectic persons.

Koch and Riddle <sup>28</sup> studied the brains of normal and ataxic pigeons and noted in the latter an increase in the content of water, protein, protein phosphorus and water-soluble phosphorus, while there was a decrease in values for lipids, cholesterol, phospholipid, sulphatide and total phosphorus.

May <sup>29</sup> showed that an experimental traumatic lesion of a cerebral hemisphere of the guinea-pig gives rise to an increase in the water, nitrogen and sulphur content and to a decrease in the phosphorus content of the disintegrating cerebral matter. In the degenerating peripheral

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26 Koch, M. L. Chemical Investigations of the Central Nervous System under Normal and Pathologic Conditions. Chemical Examination of the Central Nervous System in Two Cases of General Paralysis, *Arch. Neurol. & Psychiat.* **7** 488, 1922.

27 Singer, K. Studies on the Physiologic and Pathologic Chemistry of the Brain. III. The Phosphatides of the Petroleum Ether Fraction of the Brain in Progressive Paralysis and Marasmus, *Biochem. Ztschr.* **198** 340, 1928.

28 Koch, M. L., and Riddle, O. The Chemical Composition of the Brain of Normal and Ataxic Pigeons, *J. Comp. Neurol.* **31** 83, 1919.

29 May, R. M. Etudes microchimiques sur le système nerveux. II. L'eau, l'azote, le soufre et le phosphore cérébraux au cours de l'encephalite traumatique expérimentale du Cobaye, *Bull. Soc. chim. biol.* **11** 312, 1929.

nerves of the rabbit, May<sup>30</sup> found that the water content increased to 14 per cent above normal during the first month and then fell back to normal. The total phosphorus level diminished progressively to a third of the normal value during the first two months. The lipid phosphorus decreased to a tenth of the normal in one hundred days when histologic examination revealed complete reabsorption of the lipid products of the nerve. The protein phosphorus content, after an initial rise, fell to a third of the normal. A phosphorus fraction, the composition of which was unknown but which was soluble in alcohol and insoluble in a mixture of ether, benzene and water, fell to a third of the normal. The water-soluble phosphorus fraction increased to 25 per cent above normal during the first few days and to 35 per cent during six months. May suggested that the complex cellular constituents (phospholipids and nucleoproteins) disintegrate to form water-soluble phosphorus compounds. Degeneration of the nerve brings back the water-soluble form in which phosphorus enters the organism. There is also the possibility that the increase of water-soluble phosphorus may represent incomplete synthesis in degenerate nerves.

Degeneration of nerves seems therefore to be characterized by definite changes in the chemical composition. The content of water and protein is increased. Cholesterol is increased or remains the same. There may be an increase in cholesterol esters. Total lipids are decreased, the phospholipids to a greater extent than the cerebrosides. Water-soluble phosphorus compounds are increased.

We have undertaken this study in the hope of throwing some light on the important subject of diabetic neuritis. The cases studied were in patients of Dr Elliott P Joslin and his associates. The clinical features from a large series of cases are to be described in a separate paper. Here we merely present the results obtained in the specimens of nerves already examined chemically and try to correlate them with the clinical findings in the cases studied. The twenty specimens of nerves were obtained from eighteen diabetic patients at autopsy or after the amputation of a leg. In cases of amputation the posterior tibial nerve was selected, and at autopsy the femoral or sciatic nerve near the point of exit from the vertebral column was used. Naturally in such a small series of patients we lack certain types, especially the young person with severe diabetes.

The patients were of the arteriosclerotic type with relatively mild diabetes, the type in whom one often finds neuropathy. The ages ranged from 52 years in case 9,827 to 79.8 years in case 10,803, with

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30 May, R. M. Etudes microchimiques sur le système nerveux. III L'eau et les combinaisons phosphorées du nerf au cours de la dégénérescence, *Bull. Soc. chim. biol.* **12** 934, 1930.

an average of 66.4 years. Arteriosclerosis was present in all cases, although in case 9,827, the sclerosis was rather slight. Thirteen of the twenty nerves were taken from patients with advanced arteriosclerosis. There was deficient circulation in the legs in seventeen patients, but four had only a slight deficiency. The duration of the diabetes varied from eight-tenths year in case 11,082 to twenty-four years in case 10,964, with an average for the eighteen cases of seven and eight-tenths years. Only one patient had diabetes for less than one year, and seven had it for ten years or more. The diabetes was mild in fifteen cases and of moderate severity in three. There was no case of severe diabetes, but it is to be remarked that for several days preceding death, one patient (case 9,827), in spite of a heavy dosage of insulin, had considerable hyperglycemia due to septicemia with cavernous sinus thrombosis, although prior to the infection the diabetes had been mild and well controlled. In the sixteen cases in which we know something of the control of the diabetes prior to the condition causing admission to the hospital only three patients had poorly controlled diabetes, and in twelve the diabetes had apparently been well regulated. Unfortunately the cholesterol content was determined only in cases 3,575 and 10,964, in which the respective values were 150 and 208 mg per hundred cubic centimeters, both being within normal limits. Nor do we know the gastric acidity in all cases. The three patients tested (cases 2,629, 3,575 and 10,964) showed free hydrochloric acid. There was a history of the use of alcohol for only one patient (case 11,128) of the eleven questioned about this, and five of the other seven patients were women. A focus of infection other than the infection for which the patient entered the hospital was present in only one (case 3,575) of the fifteen examined for this condition. There was no evidence of syphilis in any case, but one patient (case 10,804) died shortly after admission and a Wassermann test was not done. Thirteen of the eighteen patients had amputations performed, in eight gangrene and in five infection was the cause of amputation. Five cases were fatal, two patients dying of infection, one of intestinal obstruction, one of coronary thrombosis and one of a combination of gangrene, infection and nephritis. Only two of the eighteen patients complained of neuritic symptoms, but it must be remembered that they were quite ill and that the existing illness probably obscured many minor symptoms. In case 10,804 there was complaint of pain in the legs and in case 11,106 of cramps in the legs. Owing to the nature of the lesions of the extremities or to the emergency of the condition a neurologic examination was rarely made. However, the knee jerks, tested in sixteen patients, were normal in only eight. The ankle jerks were normal in only two of the twelve patients tested. All other patients tested showed hypo-activity of the

tendon reflexes. Sensation to pinprick was normal in three of the six patients so examined. The pupillary reaction was sluggish in case 11,080, and there were fixed pupils in case 11,108.

The clinical symptoms and signs in such cases under ordinary conditions will be discussed in another paper, as yet unpublished. In that article we shall describe two groups of diabetic patients similar to those studied here. One of the groups includes patients having certain neurologic changes associated with defective circulation in the legs, the second group includes those showing some evidence of chronic degenerative changes in the nerves, such as sluggish tendon jerks, paresthesia and mild pain in the legs associated with arteriosclerosis and diabetes. In the former group the average age was 58.1 years, in the latter 59.2. The average duration of the diabetes was respectively, five and four-tenths years and four and five-tenths years at the onset of the neuritic symptoms. Both groups showed arteriosclerosis and, of course, some evidence of neuropathy, because they were selected for that reason. One can see that those two groups were similar to the group discussed in the present paper, and data relating to one group probably apply roughly to the others, although the patients reported on in this paper were somewhat older and had had diabetes somewhat longer. The fact that the blood cholesterol averages in the groups in the other paper were above normal, 267 and 236 mg. respectively per hundred cubic centimeters, encourages us to believe that the chemical study of the nerves may be of importance.

For controls for the nerves from diabetic persons nerves were taken at autopsy from persons of various ages, with various diseases. These will hereafter be referred to as "normal nerves." Those used for analysis were the femoral nerves near the point of exit from the spinal cord. The extraneous tissue and fat on the outer surface of the epineurium of the nerve trunk were removed by dissection. This is not always easy, since the fat penetrates into the nerve, and this is one source of error in the determination of the total or neutral fat.

The extraction of the tissue was carried out by methods outlined by Bloor.<sup>31</sup> A weighed portion of the nerve was ground with clean sand and extracted with hot alcohol and then ether. The analyses for total lipid and phospholipid were carried out on aliquots of the alcohol-ether extracted by Bloor's methods. His technic for the colorimetric determination of total cholesterol by the Liebermann-Burchard reaction was also used. Cerebrosides were determined by Kimmelstiel's method.<sup>32</sup>

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31 Bloor, W. R. The Oxidative Determination of Phospholipid (Lecithin and Cephalin) in Blood and Tissue, *J. Biol. Chem.* **82**: 273, 1929.

32 Kimmelstiel, P. Eine Mikromethode zur Bestimmung der Cerebroside, in *Festschrift zum 60. Geburtstag von Hofrat Dr. Fritz Pregl*, Leipzig, Emil Haim & Co., 1929.

Neutral fat is a derived value obtained by subtracting the fatty acids combined in phospholipids and cerebrosides from the total fatty acids. It is assumed in these calculations that the cholesterol is all in the free state, since only traces of cholesterol ester were found at any time.

Tables 1 and 2 give the results obtained. Phospholipids in the nerves from diabetic persons were a third of the normal value. Cholesterol and cerebrosides were approximately half as high in the diabetic as in the normal nerves. Neutral fat in the diabetic nerves averaged twice the normal value.

The wide variations in the so-called normal nerves were to be expected, because of the variety of material taken for analysis. The effects of age and various diseases on the lipid content of nerves are practically unknown. These effects could not be controlled in the normal nerves.

TABLE 1—*Chemical Composition of Nerves from Normal Persons*

Nerve	Neutral Fat		Phospholipid		Cholesterol		Cerebroside	
	Wet	Dry	Wet	Dry	Wet	Dry	Wet	Dry
Femoral	6.25		4.73		1.36		1.69	
Femoral	7.59		4.69		1.39		0.92	
Femoral	17.20	36.4	3.93	8.40	1.18	2.56	1.02	2.16
Femoral	7.60	23.8	4.34	13.63	1.39	4.35	1.50	4.70
Femoral	4.23	18.1	2.44	10.45	0.71	3.04	1.36	7.83
Femoral	4.04	14.5	3.84	13.80	1.06	3.82	1.79	6.45
Femoral	9.05	24.0	5.24	13.85	1.89	5.00	1.81	4.80
Femoral	6.76	23.9	4.48	16.40	1.40	4.25	2.38	8.63
Femoral	10.42	27.3	5.90	15.60	1.86	4.84	3.08	8.05
Average	8.35	24.0	4.40	13.15	1.36	3.98	1.73	5.80
Mean deviation	3.02	4.5	0.67	2.14	0.22	1.50	0.48	1.50
Standard deviation	4.24	6.43	0.91	2.69	0.34	2.44	0.63	1.80
Probable error	2.86	4.34	0.61	1.81	0.23	1.64	0.43	1.21

\* In this and the following tables the values for the various constituents of the nerves are expressed in per cent, or grams per hundred grams of tissue.

It appears that the essential lipid constituents of the nerves from persons with diabetes have degenerated, as shown by the decrease in the phospholipid, cholesterol and cerebroside content.

The increase of neutral fat may be the result of decomposition of phospholipid and cerebroside, although a more likely explanation seems to be the incomplete removal of the fatty tissue surrounding and penetrating the nerve. The possibility of an infiltration of fat from an extraneous source is not excluded, especially in the cases of a high fat content, and cholesterol esters may or may not have increased during the degeneration. Only traces of cholesterol esters could be found.

Bloor, Okey and Corner<sup>33</sup> found that cholesterol esters varied inversely with the activity of the corpus luteum, a high content being

33 Bloor, W. R., Okey, R., and Corner, G. W. The Relation of the Lipids to Physiological Activity. I. The Changes in the Lipid Content of the Corpus Luteum of the Sow, *J. Biol. Chem.* **86**: 291, 1930.



TABLE 2—*Chemical Composition of Nerves from Diabetic Persons*

Nerve No	Case No	Sex	Age at Death or Amputation, Years	Duration of Diabetes Mellitus, Years	Control of Diabetes Mellitus	Arterio sclerosis	Cause of Death or Amputation	Neuritic Manifestations	Nerve Analyzed	Wet Weight			
										Neutral Fat, per Cent	Phos lipid, per Cent	Choles bro side, per Cent	Cere Cent
1	2629	F	63.6	12.8	Poor	3+	Infection gangrene	Knee jerks right, absent, left, normal, ankle jerks right, absent, left, absent	Right posterior tibial	10.57	0.89	0.35	0.32
2	2863	F	61.9	9.8	Fair	3+	Infection	Knee jerks right, normal, left, normal	Left posterior tibial	6.08	1.48	0.62	1.31
3	3775	M	65.8	13.8	Good	3+	Infection gangrene, nephritis	Knee jerks right, normal, left, normal	Right femoral	4.07	1.94	1.11	0.34
4													
5	6177	F	60.0	5.0	Good	2+	Infection	Knee jerks sluggish, ankle jerks, absent	Left femoral	3.20	1.59	0.54	0.63
6	9191	F	73.2	1.9	Good	2+	Intestinal obstruction	Knee jerks normal	Right posterior tibial	9.41	1.62	0.56	0.74
7	9827	M	52.0	1.3	Good	1+	Infection	Knee jerks normal, ankle jerks ?	Left femoral	30.08	3.71	1.08	0.82
8	10791	F	73.1	10.8	Good	3+	Gangrene	Knee jerks right, absent, left, absent, ankle jerks right, absent, left, absent	Right posterior tibial	46.00	3.85	1.15	1.60
9	10803	F	79.8	2.0	Good	3+	Infection gangrene	Knee jerks right, absent, left, absent	Left posterior tibial	12.90	0.83	0.23	0.95
10	10804	F	75.4	20.0	Good	3+	Infection	Knee jerks sluggish, ankle jerks absent, leg pain	Right femoral	33.45	0.73	0.16	0.13
11	10964	F	63.6	24.0	Good	2+	Infection	Knee jerks sluggish, ankle jerks absent	Right femoral	14.65	3.94	1.22	1.13
12	10974	M	53.3	1.8	Good	3+	Infection	Knee jerks right, absent, left, absent, ankle jerks right, absent, left, absent	Right posterior tibial	56.37	1.60	0.54	0.63
13	11005	M	60.8	1.3	Good	2+	Gangrene	Knee jerks right, normal, left, normal, ankle jerks right, normal, left, normal	Left posterior tibial	4.95	1.22	0.48	0.76
14	11080	F	71.1	4.8	Poor	3+	Gangrene	Knee jerks right, sluggish, left, sluggish, pupils sluggish	Right posterior tibial	11.86	1.20	0.48	0.28
15	11082	F	68.3	0.8	Good	3+	Coronary thrombosis	Knee jerks right, normal, left, normal, ankle jerks right, normal, left, normal	Right posterior tibial	8.18	1.48	0.53	0.52
16									Right femoral	12.95	3.16	0.89	1.85
17	11106	F	66.7	14.0	Good	3+	Infection	Cramps in legs	Right sciatic	8.42	2.10	0.87	0.68
18	11108	F	73.0	10.0	Good	4+	Gangrene	Knee jerks right, normal, left, normal, ankle jerks right, absent, left, absent, pupils fixed	Left posterior tibial	18.48	0.65	0.22	0.61
19	11128	M	70.3	1.0	Poor	2+	Gangrene	Knee jerks right, normal, left, normal, ankle jerks right, absent, left, absent	Right posterior tibial	14.10	1.40	0.45	1.46
20	11144	M	63.0	4.5	Good	2+	Gangrene	Knee jerks right, normal, left, normal, ankle jerks right, sluggish	Left posterior tibial	8.50	1.50	0.66	0.85
Average										7.35	1.12	0.50	0.83
Mean deviation										16.07	1.75	0.63	0.82
Standard deviation										10.40	0.79	0.24	0.33
Probable error										14.04	1.01	0.31	0.43
										9.47	0.68	0.21	0.29

characteristic of the degenerated gland. A decrease in the total cholesterol content may be compatible with an increase in the cholesterol ester. The decrease in phospholipid in this group of patients supports the hypothesis that the phospholipid content is a function of physiologic activity. Free cholesterol and cerebroside appear to vary directly with the activity of the tissue.

In an examination of the chemical findings with respect to clinical features, we noted some points of interest, although data based on such a small series may not be entirely reliable.

As table 3 shows, age alone seems to affect the results very little, in contrast to Marton's<sup>34</sup> observation that irritability of the nerves decreases as age increases. The highest phospholipid, the highest chole-

TABLE 3—*Average Values with Respect to Age*

Age	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
50 to 60 years	2	2.54	0.82	1.18
60 to 70 years	11	1.58	0.61	0.75
70 to 80 years	7	1.94	0.62	0.85
Normal average		4.40	1.36	1.73

TABLE 4—*Average Values with Respect to Arteriosclerosis*

Arteriosclerosis	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
1+ (slight)	1	3.85	1.15	1.60
2+	6	1.69	0.64	0.69
3+	12	1.67	0.60	0.77
4+ (advanced)	1	1.40	0.45	1.46
Normal average		4.40	1.36	1.73

sterol and the fifth highest cerebroside value were observed in the second oldest patient, whereas the second lowest phospholipid and the lowest cholesterol and cerebroside content were encountered in the oldest patient. The range of ages lay between 52 and 79.8 years, and we have therefore divided the patients into three groups: from 50 to 60 years, from 60 to 70 years and from 70 to 80 years.

Arteriosclerosis may be an important factor, since the fat values other than those of cerebroside dropped as the arteriosclerosis increased. Yet it must be said that we had only one patient with 1+ arteriosclerosis and one with 4+ and that the difference between the moderate and the more advanced class was very slight. Table 4 shows the comparison.

34 Marton, S. Ueber verminderte Nervmuskelerregbarkeit bei Diabetes, Wien Arch f inn Med 16: 309, 1929.

Another way of demonstrating the relationship to vascular disease is to compare the results with circulatory deficiency in the lower parts of the legs as judged by the method described by McKittrick and Root<sup>35</sup> It seems unlikely that the circulatory deficiency noted in the lower parts of the legs extended as high as the pelvis One is more inclined to view this feature as merely added evidence of arterial disease, which itself affected the nerves at higher levels The fall in the lipid values with the increasing circulatory disturbance is striking, as portrayed in table 5, but the difference is apparently due in part to the level of the section of the nerve examined

TABLE 5—*Average Values with Respect to Circulatory Deficiency in the Lower Parts of the Legs*

Circulatory Deficiency	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0	1	3.85	1.15	1.60
1+	4	2.59	0.85	1.01
2+	8	1.69	0.62	0.80
3+ (seven)	7	1.19	0.45	0.63
Normal average		4.40	1.36	1.73

TABLE 6—*Average Values with Respect to Proximal and Distal Nerves*

Level of Nerve	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Pelvis	7	2.90	0.98	1.01
Lower part of leg	13	1.21	0.44	0.70
Normal average		4.40	1.36	1.73

Still another method of determining the effect of the vascular disease is to compare the values for the posterior tibial nerves with those for the femoral and sciatic nerves at the level of the pelvis, because, as is well known, the effect of arteriosclerosis is more evident in the distal than in the proximal parts There is a marked decrease of the lipid content of the tibial nerves as compared with that of the upper nerve trunks This is in line with the statement of Pyce<sup>36</sup> that the posterior tibial artery seems peculiarly susceptible to arteriosclerosis

This is in accordance with the statement that the ankle jerks are affected sooner and usually to a greater extent than the knee jerks It also bears out the statement of Auché<sup>4</sup> and Woltman and Wilder<sup>37</sup> that the distal portion of the nerve is more damaged than the proximal In this connection, a comparison of the values for the femoral and sciatic nerves in case 11,082, in which the knee jerks and ankle jerks and sensation to pinprick were normal, is interesting

<sup>35</sup> McKittrick, L. S., and Root, H. F. *Diabetic Surgery*, Philadelphia, Lea & Febiger, 1929

The figures given in table 7, with the exception of the value for the cerebroside in the femoral nerve, are definitely below the average normal values, although the patient exhibited no neuritic manifestations. This suggests that changes occur in the nerves before clinical evidence of neuritis is noted. In table 8 it can be seen again that in spite of normal tendon jerks the nerve on which the reflex depends shows a considerable degree of change. As would be expected, the greater the clinical evidence of neuropathy, the greater the chemical change.

TABLE 7—*Comparison of Femoral and Sciatic Nerves in Case 11,082*

Nerve	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Femoral (right)	3.16	0.89	1.85
Sciatic (right)	2.10	0.87	0.68
Normal average	4.40	1.36	1.73

TABLE 8—*Average Values with Respect to Absence or Normality of Reflex*

Condition of Reflex	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Normal	4	2.54	0.83	0.91
Absent (exclusive of 2 cases)	5	1.40	0.51	0.80
Absence of both knee jerks and both ankle jerks	2	0.98	0.32	0.45
Normal average		4.40	1.36	1.73

TABLE 9—*Average Values with Respect to Severity of Diabetes*

Severity of Diabetes	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Mild (17 cases)	1.87	0.64	0.82
Moderate (3 cases)	1.39	0.59	0.81
Normal average	4.40	1.36	1.73

\* There being no standard for judging the severity of diabetes, we have used the following arbitrary standard, with consideration of the rapidity of changes in the blood sugar, the size of the patient, etc.: mild, requiring no insulin or no more than 10 units a day, moderate, requiring from 10 to 30 units a day, and severe, requiring more than 30 units a day, with an adequate diet with from 120 to 180 Gm. of carbohydrate.

In comparing the chemical values with the diabetes itself, the fact that we classify the neuropathy as diabetic implies that the duration, the severity or the control of the diabetes should exert some influence on the changes noted. Marton<sup>34</sup> found decreased irritability of the nerves in proportion as the duration of the diabetes increased. As a matter of fact, the changes we noted seem only slightly dependent on these factors, possibly because we have too few cases for comparison. Nevertheless the results are compatible with the fact that diabetic neuritis is rarely observed in diabetic children, who are most severely afflicted with the disease and in whom the disease is less often well regulated.

The most that one can say about the effect of the diabetes is that those patients having the disease less than two years show less changes on the average than those having it longer, that those in whom the diabetes is mild show slightly less change than do the patients with a moderately severe case, and, finally, that those in whom the diabetes has been well controlled have average values more nearly approaching normal than the patients in whom the diabetes has not been properly regulated. But in each group marked variations occur at times, possibly owing to the influence of factors other than the diabetes and in par-

TABLE 10—Average Values with Respect to Duration of Diabetes

Duration	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
0 to 2 years	8	2.18	0.72	0.87
2 to 10 years	5	1.42	0.53	0.97
10 to 24 years	7	1.62	0.60	0.66
Normal average		4.40	1.36	1.73

TABLE 11—Average Values with Respect to Previous Control\* of Diabetes

Control	Number of Cases	Phospholipid, per Cent	Cholesterol, per Cent	Cerebroside, per Cent
Good	14	1.86	0.65	0.87
Fair	1	1.48	0.62	1.31
Poor	3	1.29	0.51	0.56
Normal average		4.40	1.36	1.73

\* For an estimation of the control of diabetes we have used our records plus statements from the patients as to previous glycosuria. Specimens taken at the time of admission are not reliable, because at such times the diabetes is upset by the condition leading to amputation or death. If the urinary sugar was less than 1 Gm. per hundred cubic centimeters or the blood sugar less than 200 mg. and no increase in the dosage of insulin or decrease in carbohydrates in the diet was made, the diabetes was considered adequately controlled. As a matter of fact, we do not know that the diabetes was well controlled in any case, because we have no record of repeated, daily blood tests and urinalyses over a long period prior to the amputation or autopsy. Even if the blood sugar is practically normal and there is no glycosuria, there may be abnormal fat metabolism as evidenced by hypercholesteremia. We do not wish to convey the impression that we believe the diabetes has no effect in the production of the neuritic changes.

ticular to the level of the nerve section examined and the nerve used. Femoral nerves probably have a lipid content different from that of posterior tibial nerves.

#### SUMMARY AND CONCLUSIONS

1 The amounts of various lipid constituents of nerves from persons with diabetes were determined and compared with those of nerves from nondiabetic persons.

2 The phospholipid, cholesterol and cerebroside values of diabetic nerves were found to be considerably below the averages found in the "normal" nerves used for controls.

3 The greater the vascular disease present and the lower the level of the nerve examined, the more marked were the chemical changes.

4 The effect of the severity, duration and control (as judged by glycemia and glycosuria) of the diabetes was slight or vitiated by other factors

5 Occasionally marked variation occurred, unexplainable on the basis of vascular disease or of the known features of the diabetes (case 10,804)

6 The lipoid abnormality appeared in the absence of clinical evidence of neuropathy, but the degree of the abnormality increased as the clinical signs of neuropathy progressed

7 The small number of cases and the many variables make the deductions unreliable. Subsequent work is being carried on to correct this

# STUDIES ON THE CORONARY CIRCULATION

## III EFFECT OF INTRAVENOUS INJECTIONS OF DEXTROSE ON THE CORONARY CIRCULATION

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AND

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The intravenous administration of dextrose has become an important therapeutic procedure. The use of dextrose in shock accompanying coronary thrombosis and in other forms of medical shock is now rather widespread. Marvin<sup>1</sup> recently reported that injections of dextrose have been effective in the treatment of heart failure and cardiac disturbances brought about by diphtheria. Edwards and Page<sup>2</sup> showed that intravenous injections of dextrose produce marked improvement in the action of hypodynamic hearts of dogs suffering from hypoglycemia produced by insulin. Middleton and Oatway<sup>3</sup> found that diabetic patients suffering from anginal pains were frequently hypoglycemic or that the sugar level was below that usually found in diabetic patients. Root and Graybiel<sup>4</sup> reported that in some patients the anginal pains are relieved by the intravenous injection of a solution of dextrose (20 cc of a 50 per cent solution). Strouse, Soskin, Katz and Rubinfeld<sup>5</sup> reported that in diabetic patients hypoglycemia induced either by insulin or by a diet low in carbohydrates produced deleterious effects on the heart and, in some patients, caused anginal pains. The administration of dextrose was found to improve the condition in some cases. Smith,

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From the Departments of Medicine and Physiology, University of Kansas School of Medicine

1 Marvin, H M. Personal communication to the authors

2 Edwards, D J, and Page, I H. Observations on the Circulation During Hypoglycemia from Large Doses of Insulin, *Am J Physiol* **69** 177, 1924

3 Middleton, W S, and Oatway, W H. Insulin Shock and the Myocardium, *Am J M Sc* **181** 39, 1931

4 Root, H F, and Graybiel, A. Angina Pectoris and Diabetes Mellitus, *J A M A* **96** 925 (March 21) 1931

5 Strouse, S, Soskin, S, Katz, L N, and Rubinfeld, S H. Treatment of Older Diabetic Patients with Cardiovascular Disease, *J A M A* **98** 1703 (May 14) 1932

Gibson and Ross,<sup>6</sup> working with nondiabetic patients suffering from cardiac failure, observed beneficial effects from the administration of an increased amount of carbohydrate. They attributed the improvement to the easily available energy of the carbohydrates. Sprague and Camp<sup>7</sup> used hypertonic solution of dextrose intravenously in the treatment of nineteen cases of cardiac disease. They reported good results in patients suffering from paroxysmal dyspnea and cardiac asthma. Reports of successful treatment of conditions involving circulatory disturbances by intravenous injections of dextrose are numerous.

It seemed to us that further experimentation for the purpose of determining the cause of the beneficial results following the administration of dextrose might be valuable. In our recent work on the effect of various chemical agents on coronary circulation, we have become interested in the length of time that the coronary circulation is influenced by the drug as well as by the amount of change produced. It would seem that the beneficial action of any drug used to improve coronary circulation would be derived from a sustained increase rather than from a sudden increase of short duration. Epinephrine produces a sudden and marked increase in the coronary flow, but the effect is very brief. Levine, Ernstene and Jacobson<sup>8</sup> found that patients suffering from angina pectoris experienced typical pains following the administration of epinephrine. Even though there is a sudden dilatation of the coronary vessels, observed experimentally following the administration of epinephrine, the constriction which follows seems to be the cause of the anginal pain in patients suffering from angina pectoris.

#### METHODS

Our first series of experiments was conducted on the whole animal under uniform ether anesthesia. The method was the same as that previously described by us.<sup>9</sup> The Morawitz cannula was somewhat modified in that the inner brass tube was transferred to the wall of the cannula, thus permitting a freer flow of blood and less likelihood of the formation of a fibrin clot in the cannula. Pure gum tubing with a wall thickness of  $\frac{1}{32}$  inch (0.08 cm) was used for valve material. The valve was sufficiently short that no obstruction of flow into the sinus occurred except from the posterior cardiac vein.

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6 Smith, F. M., Gibson, R. B., and Ross, N. G. The Diet in the Treatment of Cardiac Failure, *J. A. M. A.* **88** 1943 (June 18) 1927.

7 Sprague, H. B., and Camp, P. D. Intravenous Hypertonic Glucose in the Treatment of Cardiac Disease, *New England J. Med.* **206** 288, 1932.

8 Levine, S. A., Ernstene, A. C., and Jacobson, B. M. The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, *Arch. Int. Med.* **45** 191 (Feb) 1930.

9 Ginsberg, A. M., and Stoland, O. O. The Effect of Glycocyamine on the Coronary Circulation, *J. Pharmacol. & Exper. Therap.* **41** 195, 1931.



An anticoagulant from dog liver was used, larger amounts were necessary following the administration of dextrose on account of the increased coagulability induced by the dextrose. Control experiments have convinced us that by this method the coronary flow remains nearly uniform for at least forty minutes, provided the artificial respiration is properly adjusted. In our latest experiments, the blood pressure was maintained at a constant level by a compensator.

Experiments were carried out on twenty-eight dogs. The dextrose used was a 50 per cent solution. It was introduced through the return flow cylinder attached to the femoral vein. Injection at the rate of 2.5 Gm per minute produced no appreciable change in the blood pressure. Determinations of the blood sugar were made by the Folin-Wu method.

The second series of experiments was conducted on the denervated heart-lung preparation described by Knowlton and Starling<sup>10</sup>. Several innervated heart-lung preparations, following the method of Anrep and Segall,<sup>11</sup> were also used.

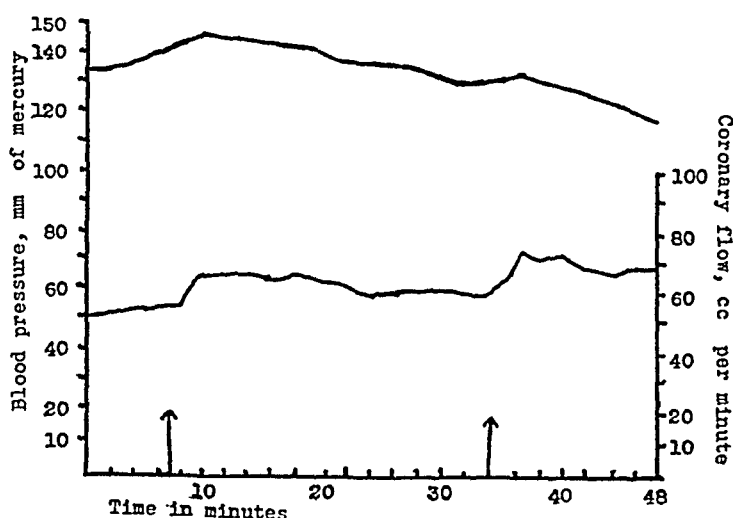


Fig 1—Blood pressure (upper curve) and coronary sinus flow (lower curve) in an intact animal. At the arrows 5 Gm of dextrose (10 cc of a 50 per cent solution) was injected, showing that a second injection of dextrose is as effective as the first in increasing the coronary circulation.

## RESULTS

*On the Whole Animal*—The results of our experiments on the whole animal are recorded in table 1. In figure 1 the results of a typical experiment show that the increased flow of blood from the coronary sinus occurs even when the blood pressure is somewhat lower than the preinjection level. In most of the experiments the blood pressure was slightly increased following the injection of dextrose.

It will be seen that the rate of output from the coronary sinus was increased in every case. The maximum increase occurred in from two

10 Knowlton, F. P., and Starling, E. H. The Influence of Variations in Temperature and Blood-Pressure on the Performance of the Isolated Mammalian Heart, *J. Physiol.* **44** 206, 1912-1913.

11 Anrep, G. V., and Segall, H. N. The Central and Reflex Regulation of the Heart Rate, *J. Physiol.* **61** 215, 1926.

to forty-one minutes after the injection of dextrose. In most of the experiments the amount of dextrose used was 5 Gm in a 10 cc solution. In most of them the coronary flow did not return to the preinjection level in forty minutes or more. When repeated injections were made, the second injection produced as great an increase as or even a greater one than that which followed the first injection. These results, we

TABLE 1—*Effect of Dextrose on the Coronary Circulation of Intact Dogs\**

Dog	Weight, Kg	Date	Normal Coro- nary Flow, Cc per Minute	Maximum Flow		Maximum Percentage Increase in Flow†	Amount of Dextrose Injected, Gm	
				Cc per Minute	Time After Injection, Minutes			
1	8.6	5/ 1	21	40	22	90.4	10	
2	10.0	5/ 8	28	47	5	67.8	10	
3	10.2	5/13	28	51	3	82.1	10	
4	5.5	6/10	20	52	6	160.0	10	
5	9.5	6/11	54	95	13	75.9	7	
6	8.2	6/13	26	38	3	46.1	5	
			32	50	8	56.2	5	(second injection)
7	10.5	6/14	41	60	5	46.3	5	
			41	62	11	51.2	5	(second injection)
8		6/15	28	35	4	25.0	5	
			28	44	6	57.1	5	(second injection)
9	6.4	6/16	24	43	3	79.1	5	
10	7.2	6/17	18	43	20	138.8	5	
11	10.4	6/18	44	72	16	63.6	5	
12	13.7	6/20	32	67	7	109.3	5	
13	8.2	6/21	39	90	41	130.7	5	
14	7.3	6/23	21	39	7	85.7	5	
15	8.2	6/24	35	74	32	111.4	5	
16	10.4	6/29	49	54	6	10.2	5	
			50	65	5	30.0	5	(second injection)
17	9.5	7/14	55	134	22	143.6	5	
18	10.0	4/21	33	74	14	124.2	5	
19	8.1	11/20	17	27	2	58.0	5	
			18	32	2	77.0	5	(second injection)
20	10.4	10/17	67	98	5	46.0	5	
			42	65	10	54.0	5	(second injection)
21	10.4	4/22	21	48	36	128.5	5	
22	9.5	4/24	30	38	2	26.6	5	
23	9.1	4/25	14	20	8	30.0	5	
24	10.9	5/ 2	18	25	2	28.0	5	
			21	39	7	85.7	5	(second injection)
25	8.5	5/ 4	37	60	7	62.1	5	
			39	64	5	64.1	5	(second injection)
26	9.3	8/18	23	26	9	13.0	5	
			25	29	3	16.0	5	(second injection)
27†	9.5	8/17	41	55	4	31.8	5	
28†	11.3	8/17	57	68	3	19.3	5	
			61	74	3	21.3	5	(second injection)
29†	11.8	8/21	65	90	4	38.4	5	

\* A 50 per cent solution of dextrose was injected intravenously at the rate of 5 cc per minute.

† The average percentage increase in coronary blood flow with 5 Gm of dextrose (twenty-four dogs) equaled 66.48 and on the second injection (ten dogs), 51.26. The average percentage increase in coronary blood flow with 10 Gm of dextrose (four dogs) equaled 100.07.

‡ In this experiment the blood pressure was maintained at a uniform level near normal during the period of experimentation.

believe, are of paramount importance for they show that injections of dextrose do not render the coronary mechanism incapable of responding to the further administration of dextrose. The results point further to the possibilities of the intravenous administration of dextrose as a means of maintaining a sustained increased flow in the coronary circulation without noticeable changes in either the heart rate or the blood pressure.

The results of a typical experiment with repeated injections of dextrose are shown in figure 1. The amount of dextrose injected is apparently a factor in increasing the coronary circulation, since 10 Gm usually produced a greater increase in flow than was produced by the injection of 5 Gm. In one experiment the injection of 25 Gm of dextrose increased the coronary flow from 25 to 92 cc per minute four minutes after the injection was completed.

These results seem to justify the following conclusions concerning the intravenous administration of dextrose as a means of increasing the coronary circulation in the intact animal. 1 The increase is very marked, ranging from 10 to 100 per cent or more. 2 The increased rate of flow is maintained for a long period, forty minutes or more. 3 Repeated injections continue to be effective in increasing the coronary flow.

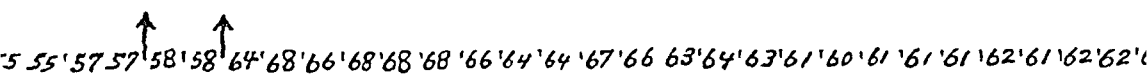


Fig 2—Blood pressure and coronary sinus output of dog weighing 11.3 Kg while under ether anesthesia. Between the arrows, 5 Gm of dextrose (50 per cent solution) was injected intravenously. The figures on the baseline indicate the coronary sinus flow in cubic centimeters per minute. The blood pressure was maintained at a uniform level by means of a pressure compensator.

4 The amount and rate of injection produced no undesirable physiologic reaction, provided the rate of injection was not more than 2.5 Gm per minute. In some of our experiments more rapid injections, up to 10 Gm per minute, produced a temporary fall in blood pressure. In this experiment a fall of blood pressure from 80 mm to 60 mm of mercury occurred, but the blood pressure promptly returned to normal. These results indicate that when 50 per cent solutions of dextrose are administered intravenously, the injection should be made at a slow rate.

In three experiments, the blood pressure was maintained at a uniform level by means of a compensator. The results were not appreciably different from those in which the blood pressure was not controlled, and

indicate that the increased coronary flow following injections of dextrose could not be attributed to a change in the blood pressure. The results of such an experiment are shown in figure 2.

*On the Denervated Heart-Lung Preparation*—The effect of dextrose on six heart-lung preparations was determined. The solution of dextrose was added to the blood in the venous reservoir in amounts equivalent to that used in the whole animal. The results obtained on the heart-lung preparations are recorded in table 2. In two of the experiments the coronary flow was slightly increased by the introduction of dextrose, but in the other four the flow was unaltered or decreased. In two of the experiments, when the heart rate was determined the rate increased at the same time that the coronary flow decreased following

TABLE 2—*Effect of Dextrose on the Coronary Circulation of Denervated Heart-Lung Preparations\**

Experiment	Weight, Kg	Date	Normal Coronary Flow, Cc per Minute	Maximum Change in Flow		Maximum Percentage Change in Flow		Amount of Dextrose Injected, Gm
				Cc per Minute	Time After Injection, Minutes	Increase	Decrease	
1	19.0	2/21	42	47	12	11.9		1.5
2	23.6	2/22	34	37	4	8.8		1.5
3	16.7	3/21	40	40				1.5
4	10.2	3/28	51	42	11		17.6	1.5
			42	42				1.5 (second injection)
5†	22.2	6/28	97	86	10		11.4	1.5
			86	80	1		6.9	1.5 (second injection)
6†	17.1	6/29	100	85	12		15.0	2.5
			85	80	2		5.8	2.5 (second injection)
Average							4.0	

\* A 50 per cent solution of dextrose was injected into the venous reservoir, except in experiment 2 in which the injection was given directly into the venous cannula.

† Changes in the heart rate were determined; the heart rate increased from 12 to 24 beats per minute after the injection of dextrose.

the injection. The results indicate that dextrose has no dilator action on the coronary vessels which could account for the increased coronary circulation in the whole animal.

Hydremia, caused by the hypertonic solutions of dextrose, might by decreasing the viscosity of the blood account for the augmented coronary flow in the whole animal. Kinsman, Spurling and Jelsma<sup>12</sup> and others have shown that there is a marked decrease in the specific gravity of the blood following injections of hypertonic solutions of dextrose. The fact that the specific gravity increased very suddenly and returned to normal twenty minutes after the injection of hypertonic solution while the increased coronary flow came on gradually and lasted much longer indicates that the increased coronary flow following the

12 Kinsman, J. M., Spurling, R. G., and Jelsma, F. Blood and Cerebro-Spinal Fluid Changes After Intravenous Injections of Hypertonic Solutions, *Am J Physiol* **81** 165, 1928.

administration of dextrose in the whole animal cannot be fully accounted for by this factor

The viscosity of the blood was determined in two experiments. There was a slight decrease in viscosity after the injection of the hypertonic solution of dextrose, but the viscosity soon returned to the preinjection level before the maximum coronary flow developed.

That the increased coronary circulation in the whole animal following the injection of dextrose is only partially accounted for by drawing fluids from the tissues into the blood was further demonstrated by the

TABLE 3—*Effect of Dextrose on the Coronary Circulation in Innervated Heart-Lung Preparation\**

Experiment	Weight, Kg	Date	Normal Coronary Flow, Cc per Minute	Maximum Change in Flow		Maximum Percentage Change in Flow		Place of Injection of 1.5 Gm Dextrose
				Cc per Minute	Time After Injection, Minutes	Increase	Decrease	
1	17.2	7/30	41	45	1	9.7		Cerebral circulation
			42	46	2	9.5		Cerebral circulation (second injection)
			43	39	5		9.3	Cardiac circulation (third injection)
2	16.0	8/11	43	38	7		11.6	Cerebral circulation
			41	43	2	4.8		Cardiac circulation (second injection)
3	10.9	8/12	55	53	6		3.6	Cardiac circulation
			52	48	9		7.6	Cerebral circulation (second injection)
4	14.0	8/14	55	59	1	7.2		Cerebral circulation
			63	57	4		9.5	Cardiac circulation (second injection)
Average							1.15	
After Cutting Vagi								
1	17.2	7/30	71	75	2	5.6		Cerebral circulation
2	16.0	8/11	97	105	1	8.2		Cerebral circulation
3	10.9	8/12	63	58	6		7.9	Cardiac circulation
Average							1.9	

\* One and five tenth grams of a 50 per cent solution of dextrose was injected as designated

injection of isotonic solutions of sodium chloride and dextrose. In two experiments the injection of 100 cc. of a 0.9 per cent solution of sodium chloride caused practically no change in the coronary circulation, a corresponding injection of isotonic solution of dextrose in four animals produced an average increase of 34.2 per cent in the coronary circulation.

Hypertonic solution of sodium chloride (10 cc. of an 8 per cent solution) in five animals produced a 30 per cent increase in the coronary flow, while an equivalent amount of hypertonic solution of dextrose (50 per cent) produced an increase of 58.75 per cent in the coronary flow. These results indicate that the increased coronary flow following injections of dextrose cannot be fully accounted for by the hydiemia and lowered viscosity of the blood. It is apparently one important factor

*On the Innervated Heart-Lung Preparation*—Several innervated heart-lung preparations were utilized to determine whether the improved coronary circulation following injections of dextrose was caused by the action of dextrose on the nerve centers. In these experiments the method described by Anrep and Segall<sup>11</sup> was used, except that the cerebral circulation was allowed to return directly to the heart. The cerebral circulation was maintained at a uniform pressure throughout the experiments, and the presence of the corneal reflex showed that adequate circulation was maintained through the brain. Sodium amytal was used as the anesthetic.

An increased coronary flow which followed cutting of the vagus nerves indicated that the tonic coronary constrictor action of the vagus mechanism was active during the experiment. The results obtained in these experiments are recorded in table 3. The amount of dextrose injected corresponded to that used in the denervated heart-lung prepara-

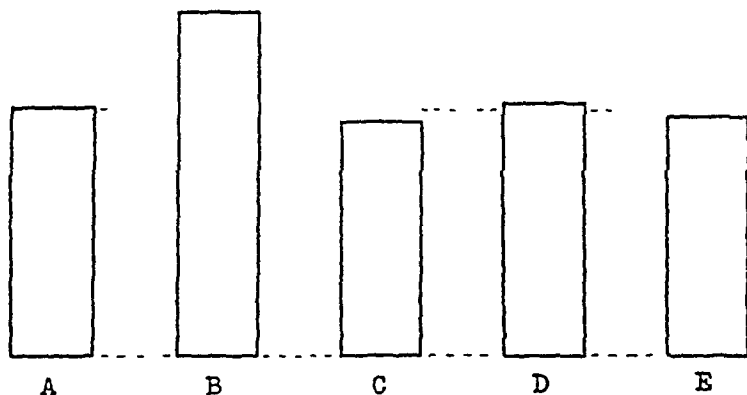


Fig 3—A comparison of the effect of injections of dextrose on the coronary flow. *A*, normal coronary sinus output, *B*, coronary sinus output ten minutes after an injection of dextrose into an intact animal, *C*, same as in *B*, for a denervated heart-lung preparation, *D*, same as in *B*, for an innervated heart-lung preparation, *E*, same as in *B*, for an innervated heart-lung preparation with both vagus nerves cut.

tions and was about equivalent to that used in the intact animal on the basis of the volume of circulating blood.

As will be seen from the table, there was no appreciable change in the coronary flow following the injections of dextrose into the cerebral or cardiac circulation. A slight increase occurred one or two minutes after the injection, when the coronary flow returned to the former level. These results show that the increased coronary flow in the intact animal following the administration of dextrose is not caused by the action of dextrose on nerve centers.

*Comment*—A comparison of the normal coronary blood flow with the coronary flow of the intact animal and of the denervated and innervated heart-lung preparations following injections of dextrose is shown

in figure 3. These results show conclusively that dextrose has no direct effect on the coronary vessels or on the nervous centers. The improvement of the coronary circulation in the intact animals and in the various types of patients must be the result of other factors.

The blood sugar values were determined in a number of experiments. In three experiments we found an increase of 5.7 mg per hundred cubic centimeters of blood in a ten minute period as a result of the ether anesthesia. Injection of an anticoagulant from dog liver in amounts equivalent to that used in the experiments on the coronary circulation produced a rise of 7.16 mg of blood for a ten minute period. In control experiments on the coronary circulation the blood sugar level rose 10.68 mg in ten minutes. Following the injection of 5 Gm of dextrose in the whole animal which caused an increase in coronary circulation, the blood sugar level was increased an average of 75.2 mg ten minutes after the injection. In heart-lung preparations, when we introduced dextrose in amounts equivalent to that used in the whole animal the blood sugar level increased 122.87 mg per hundred cubic centimeters of blood ten minutes after the dextrose was added to the blood in the venous reservoir. Since the highest blood sugar level was attained in the heart-lung preparations, in which we found no increase in the coronary circulation, it is apparent that the high blood sugar level has no effect on the coronary vessels.

The improved coronary circulation observed in the intact animal is undoubtedly caused to a large extent by the increased water content of the blood. Since the increase does not occur in heart-lung preparations, it seems justifiable to assume that the hydremia is due to drawing water from the abdominal and other organs rather than from the heart and lungs. While our results do not prove conclusively that the entire increase is due to the hydremia of the blood, other possible causes have been ruled out. For some reason the hydremia produced by hypertonic solution of dextrose is more effective in increasing the coronary circulation than that produced by injecting hypertonic or isotonic solutions of sodium chloride.

#### SUMMARY AND CONCLUSIONS

1. The effect of intravenous administration of dextrose on the coronary circulation has been determined on the intact animal and on denervated and innervated heart-lung preparations before and after cutting of the vagus nerves.

2. Intravenous injection of 5 Gm of dextrose in a 50 per cent solution produced a marked and sustained increase in the coronary circulation of the intact dog under ether anesthesia.

3. Hypertonic solution of dextrose in amounts equivalent to that used in the intact animal produces no significant change in the coronary flow of denervated or innervated heart-lung preparations.

4 Repeated injections of dextrose are effective in increasing the coronary flow of intact animals

5 Part of the increase in the coronary flow can be accounted for by the increased water content of the blood, the water being drawn mainly from organs other than the heart and lungs

6 That the increased flow is not due to a reflex involving the nerve centers is evident by the fact that in the innervated heart-lung preparations no increase in the coronary flow followed injections of dextrose

7 The sustained increase in the coronary flow in the intact animal and the absence of undesirable physiologic reactions following the administration of hypertonic solutions of dextrose may account for many favorable clinical results reported and also suggest its use as a therapeutic agent for patients requiring improvement in the coronary circulation



# FRAGILITY AND MATURATION OF RETICULOCYTES

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AND

W DOCK, M D

SAN FRANCISCO

The experimental observations reported here were designed to give additional information as to the relative ability of the reticulocytes to withstand such hemolytic substances as saponin in the living animal and in shed blood and to determine the rate and extent to which they mature into nonreticulated cells. These points were considered of importance in connection with the validity of the two current theories as to the origin of macrocytic hyperchromic (addisonian or pernicious) anemias. The maturation theory ascribes the disease to the absence of sufficient quantities of a substance needed for the maturation and release of the red cells, the hemolytic theory ascribes the disease to the action of an absorbed hemolytic agent. Since neither theory is adequately proved, it seemed desirable to know more about the properties of the curious vital-staining cells, the sudden increase of which, in spontaneous and induced remissions of macrocytic anemia, is such a significant phenomenon. Similar but less striking increases occur in anemia due to a deficient absorption of iron when iron is supplied. The reticulocytes are present in unusual numbers in all of the anemias known to be of hemolytic origin but are not numerous during relapses of primary anemia.

## METHODS

Reticulocytes in abundance are present in the blood of rats kept for three or four days at barometric pressures of from 300 to 400 mm of mercury. The blood, treated with an anticoagulant from dog liver or oxalate or defibrinated by being shaken with glass beads, was used for the study of hemolysis in vitro, and wet preparations stained with brilliant cresyl blue were used for reticulocyte counts. Washed red cells and varying amounts of plasma from the same animal were added to tubes with from 0.2 to 1.4 mg of saponin per hundred cubic centimeters. The volume of cells was 0.2 cc, the total volume in each tube was 2.5 cc. The smears were made from tubes showing partial hemolysis. The reticulocyte percentage was based on a count of at least 1,000 red cells.

Rabbits were used for the experiments on the action of saponin on the reticulocytes in circulating blood. The solution was injected intravenously, and reticulocyte counts were made on wet preparations of blood taken from the small ear veins at intervals thereafter.

## EXPERIMENTAL RESULTS

*Resistance of Reticulocytes to Saponin and to Hypotonic Salt—*

When the red blood cells of a rat are washed with a 0.9 per cent solution of sodium chloride three times and then suspended in weak saponin solutions at icebox temperature for from twelve to eighteen hours, there is a decrease in relative percentage of reticulocytes in the dilution in which partial hemolysis takes place. This also is observed in blood

TABLE 1—*The Effects of Saponin During Twenty-Four Hours in the Icebox on the Percentage of Reticulocytes in the Blood\**

Blood	Concentration of Plasma, per Cent of Cell Volume	Concentration of Saponin, Mg per 100 Cc	Reticulocyte Count	
			Control, per Cent of Total Red Blood Cells	Saponin, per Cent of Total Red Blood Cells
Rat 1	0	0.4	14	2.2
Rat 2	0	0.6	4	1.8
Rat 3	0	0.9	14	9.5
	33	1.0	13	44.5
Rat 4	30	0.8	30	60
Rat 5	10	0.6	29	12
Rat 6	50	1.0	10.9	27
	25	1.0	10.4	30
	10	0.8	4	5
Rat 7	30	1.1	8.8	36
	0	0.6	9.0	7
	20	0.8	9.8	38
	10	0.9	8.4	27
Rat 8	200	0.8	82	100
	0	0.6	80	100
Johnson primary anemia	400	1.0	36	55
	0	0.8	38	7.3
MacMahon chlorotic anemia	300	1.0	5.2	4.2
	0	1.0	6.0	1.2
Rat 12 (37° C.)	30	1.0	11.0	4.2
Rat 13 (37° C.)	30	1.0	14.5	5.8

\* Rat 2 was normal, and rat 8 had anemia due to Bartonella and splenectomy. All of the others had been under low barometric pressure for from four to six days. The patient's blood was obtained during the response to therapy. At the temperature of the icebox the reticulocytes were better protected by the addition of plasma to the saponin cell mixture than were the mature cells. Saponin was added to whole blood from rats 12 and 13 and incubated for eighteen hours at 37° C. Plasma failed to protect the reticulocytes.

from anemic patients with reticulocytosis due to therapy. This is the reverse of the effect of hypotonic salt, which breaks up normal cells more readily than it does the reticulocytes. It is also the reverse of the effect when whole blood or washed red cells mixed with one-tenth their volume of plasma are added to saponin solutions. In the icebox plasma protects immature red cells from saponin more effectively than it does mature cells (table 1). Only in blood with the red cells damaged by Bartonella muris (anemia five days after splenectomy) were reticulocytes found to be more resistant to saponin than were the mature infected cells.

At 37 C even the presence of the plasma fails to protect the reticulocytes from saponin. With both rat and rabbit blood the reticulocyte percentage falls when the blood which is taken with heparin or defibrinated is incubated with saponin under sterile precautions. At 37 C citrate and oxalate in the weakest anticoagulant doses cause lysis of the reticulocytes, as has previously been noted<sup>1</sup> and confirmed by us. Citrated or oxalated whole blood keeps for several days in the icebox without a change in the reticulocyte count.

*Effect of Saponin on Reticulocytes in Vivo*—The intravenous injection of from 0.2 to 0.5 mg of saponin per kilogram into the ear veins

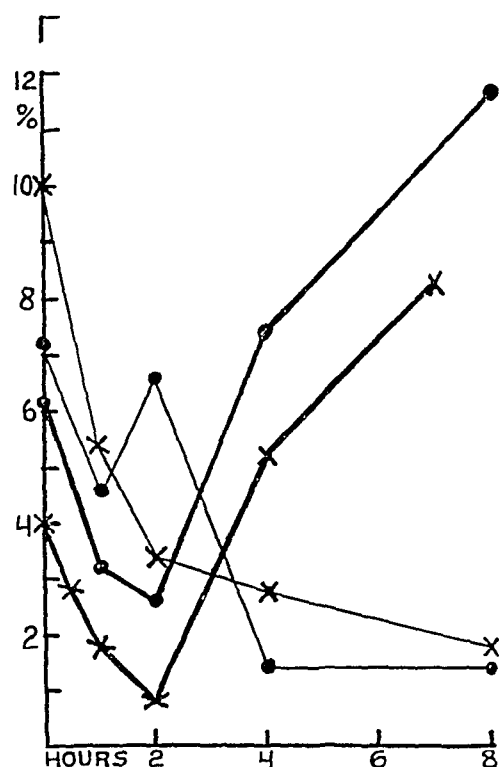


Fig 1—The effect of intravenous doses (0.5 mg per kilogram) of saponin on the reticulocyte count of rabbits. The heavy lines indicate the first injection, the light lines, a second injection twenty-four hours later. Rabbit 1 is indicated by the dots, rabbit 2, by the crosses. The fall in the reticulocyte count begins and ends much more quickly with an initial than with a second injection. Recovery from the second injection began in from thirty to fifty hours.

of rabbits causes a rapid fall, followed by a rise, in reticulocytes. If the injection is repeated within twenty-four hours, the fall continues for from eight to twenty-four hours, instead of from two to three hours, as in untreated animals, and recovery to above the initial level occurs only after from twenty-four to thirty-six hours, instead of within from

1 Pepper, O. H. P. Observations on Vitrally Stainable Reticulation in Erythrocytes Preserved in Vitro, Arch Int Med 30:80 (Dec) 1922.

four to eight hours. A test of three days between injections results in rates of fall and rise intermediate between those on initial and those on second injection, with a twenty-four hour interval (fig 1). This suggests that the lysis of reticulocytes *in vivo* is due to the activity of the animal tissues as well as to the drug, and that blocking the reticulo-endothelial cells as a result of the initial dose of hemolysant retards the speed of lysis and removal even when the effect of saponin has worn off and replacement of the reticulocytes has occurred. The importance of vital activity is seen when the rate of fall of the reticulo-

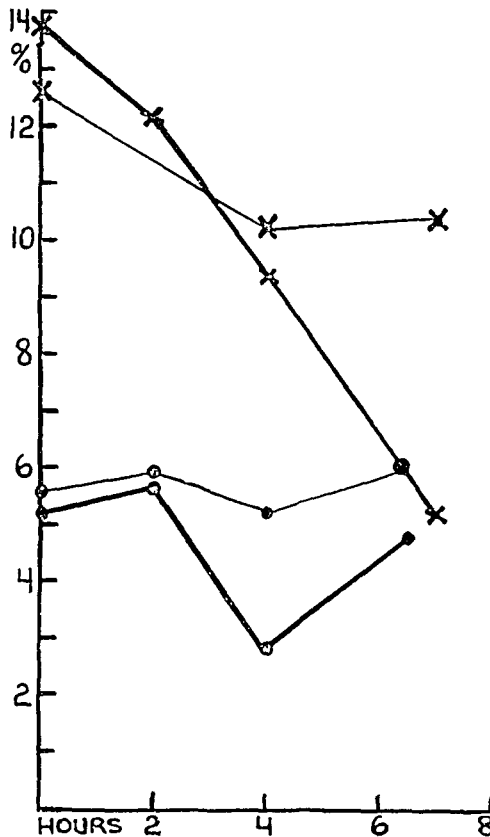


Fig 2—The comparative effect of intravenous doses of saponin on the reticulocyte counts of blood *in vivo* and *in vitro*. The heavy lines indicate *in vivo*, the light lines, *in vitro*. Five-tenth milligram of saponin per kilogram was injected immediately after the first *in vivo* count, *in vitro* counts were made at once and at intervals on 1 cc of blood treated with an anticoagulant from dog liver drawn five minutes after saponin was given and incubated at 37 C. Rabbit 3 (indicated by dots) had an injection seventy-two hours before, and rabbit 4 (indicated by crosses), an injection forty-eight hours before, so that the fall *in vivo* is slower than that occurring with an initial dose, but much greater and faster than that *in vitro*.

cytes in the blood taken at intervals after an injection of saponin is compared with the rate of the fall in the blood taken five minutes after the injection and incubated *in vitro*. Doses of saponin which are effective

in producing a prompt fall in reticulocytes in vivo have no effect if incubated with blood in vitro or cause a rate of reticulocytic lysis which is much slower than that which occurs in the circulating blood (fig 2)

*Maturation of Reticulocytes in Vitro*—Four samples of defibrinated rat blood and three of blood from treated patients with primary anemia were incubated at 37 C under sterile precautions. No evidence of the maturation of reticulocytes was found (table 2)

TABLE 2—*The Percentage of Reticulocytes in Blood Incubated at 37 C Without Bacterial Contamination*<sup>\*</sup>

	Total Reticulocytes, per Cent	Old Forms, per Cent	Intermediate Forms, per Cent	Young Forms, per Cent
Rat A				
Fresh defibrinated blood	14.6	2	2.6	10
24 hours later	16.0	0	2.0	14
Fresh citrated blood	5.0	1	4.0	
24 hours later	0.0			
Rat B				
Fresh defibrinated blood	11.2	1.0	3.0	7.2
24 hours later	12.3		4.2	8.0
48 hours later	12.8	0.4	3.4	8.2
Rat C				
Fresh defibrinated blood	10.4	0.8	3.0	6.6
24 hours later	11.6	1.9	5.7	4.0
48 hours later	13.0	1.6	9.4	2.0
72 hours later	12.0	2.4	6.8	0.8
Rat D				
Fresh defibrinated blood	12.3	1.4	2.8	8.1
24 hours later	12.1	1.0	2.6	8.5
48 hours later	12.3	2.1	2.6	6.6
72 hours later	11.8	2.0	7.2	2.6
Smith (primary anemia)				
Fresh washed citrated blood cells plus fresh serum	16.6	3.2	11.6	1.8
24 hours later	12.4	8.0	4.0	0.4
Gill (primary anemia)				
Fresh defibrinated blood	28.5	5.7	17.1	5.7
8 hours later	28.0	7.6	16.4	4.0
24 hours later	33.0	1.2	29.0	2.8
72 hours later	28.6	(faint staining, differentiation impossible)		
L. P. (primary anemia)				
Fresh defibrinated blood	24.5	3.7	12.6	8.2
18 hours later	28.8	3.3	23.2	3.3
42 hours later	14.0	2.6	10.8	0.6

\* There was no sign of maturation of young cells to old cells or of a change of reticulocytes to nonreticulocytes. The rats' polycythemic blood (counts 10,500,000 to 12,000,000) showed little serum after defibrination, while the blood from patients being treated with liver had a high plasma cell ratio. In rat A the effect of the citrate on the reticulocytes was in striking contrast with the effect of the incubation of defibrinated blood. The fresh smears stained much more rapidly than those from blood incubated more than twenty-four hours. The count on L. P., ten minutes after mixing, was only 2 per cent at forty-two hours, but rose to 14 per cent when the blood had stood more than thirty minutes.

These results contrast markedly with those of Heath and Daland<sup>2</sup> who used smears made with brilliant cresyl blue dried on the slide. These investigators<sup>3</sup> later showed that this method does not give the

2 Heath, C. W., and Daland, G. A. The Life of Reticulocytes. Experiments in Their Maturation, Arch Int Med 46:53 (Sept) 1930.

3 Heath, C. W., and Daland, G. A. Staining of Reticulocytes by Brilliant Cresyl Blue, Influence of Solutions of Substances, Arch Int Med 48:133 (July) 1931.

number of reticulocytes present but that it causes them to take up the stain easily. If one uses a wet method, as we did, the rate of staining is unimportant, as the counts are made within from twenty to thirty minutes after the cells and dye are mixed. Incubation alters the ease of staining, just as do the other methods of treatment, such as the salt solution method, which Heath and Daland studied. Hence an apparent decrease in the reticulocyte count is found when only a few seconds' staining time is permitted by the dry method.

#### COMMENT

Although casual mention of the fragility of reticulocytes in blood treated by anticoagulants has been made<sup>1</sup> and the increased fragility of blood containing young cells due to a low oxygen tension has been reported,<sup>4</sup> it is generally accepted that reticulocytes are immature but potentially sound cells. The fact that they resist hypotonic salt unusually well has created slight faith in their greater robustness. Although a few writers have regarded them as being fragile because they are immature, this has been an unsupported and unpopular notion.

We have confirmed the observation that the vitally staining red cells resist hypotonic salt and Bartonella better than do cells which do not take up the dye. We also confirmed the observation that the vitally staining red cells disintegrate more readily than do other red cells when exposed to isotonic citrate or oxalate solutions at 37 C.

In whole blood at 37 C, in suspensions of washed cells in the icebox, the greater fragility of reticulocytes in saponin solution is always apparent, but this is not true of whole blood at from 4 to 6 C. At a low temperature plasma protein protects the mature red cells less than it does the reticulocytes from saponin hemolysis. Mature washed red cells from rats with anemia due to Bartonella are also, at a low temperature, less resistant to saponin than are the reticulocytes. In dogs a prompt decrease in reticulocytes has been reported to follow intravenous injections of a saponin-like substance obtained from normal blood.<sup>5</sup>

In circulating rabbit's blood reticulocytes are far more easily destroyed by saponin injected intravenously than are the nonreticulated cells. The reticulocytes are not so rapidly destroyed when the blood treated with saponin is removed and incubated at body temperature as when the reticulocytes remain in the body. Concentrations of saponin

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4 Kaulbersz, J, and Wischnowitzer, E. Ueber die Resistenz der Blutkörperchen bei künstlich herabgesetztem Luftdruck, *Ztschr f d ges exper Med* **89** 238, 1933, Resistenz der roten Blutkörperchen und die Zahl der Reticulocyten im Hohenklima, *ibid* **87** 785, 1933.

5 Ucko, H. Ueber die hamolytisch wirkenden Substanzen des menschlichen Blutes, *Ztschr f klin Med* **118** 22, 1931.

which are met in shed blood incubated at 37 C cause a rapid decrease in the reticulocytes in vivo. Hence it is necessary to invoke the action of the reticulo-endothelial system to explain the difference in behavior of saponin-treated blood in vitro and in vivo. In every experiment in which hemolysis affected reticulocytes more than nonreticulocytes, the younger (heavily staining) cells were affected more than the old (faintly staining) reticulocytes.

Since reticulocytes are more easily destroyed than other red cells in vitro or in vivo, by various substances, some of which, like citrate and oxalate, do not have an effect on normal cells, it becomes difficult to determine whether a decrease in reticulocytes or in younger forms (since these are most susceptible) is due to destruction or maturation. In defibrinated rat blood incubated under sterile precautions for from

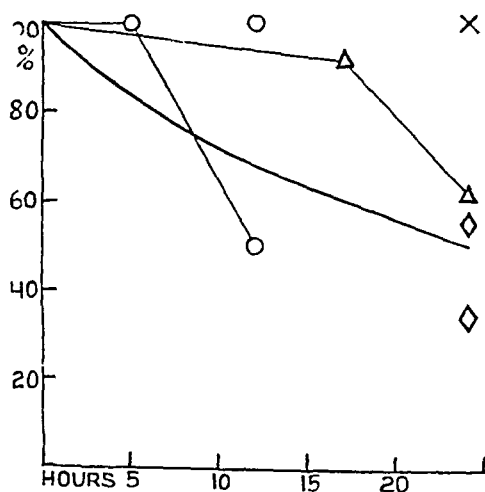


Fig. 3—The decrease in reticulocytic concentration, given in terms of per cent of the initial level, in defibrinated blood incubated at 37 C under sterile precautions. The heavy line is the theoretical curve, based on the assumption that 50 per cent of the reticulocytes mature every twenty-four hours. The fine lines indicate the distribution of recorded data. Pepper's findings are indicated by the triangles, Buckman and MacNaugher's (*J Med Research* **44** 61, 1923), by the circles, Denecke's (*Ztschr f d ges exper Med* **36** 179, 1923), by the circles and dots Heath's, by the diamonds, and Mermod and Dock's, by the cross. Two observers found no evidence of maturation or destruction of reticulocytic loss. This suggests that the change in reticulocyte count was due to lysis by the accumulation of metabolic products rather than to maturation.

two to three days there is no change in the percentage of reticulocytes or in the proportion of young and old forms, and the published records of the changes in incubated blood of man and other animals shows that no change occurs within the first five to twelve hours (depending on the observer) with a rapid fall thereafter (fig. 3). This is undoubtedly different from the logarithmic curve of growth or maturation, and suggests that with incubation toxic substances may accumulate to

which reticulocytes, especially the young forms are more susceptible than red cells in general. The change in the proportion of young and old forms, after the peak of rise in the treatment of primary anemia may also be due to the relatively short survival time of young reticulocytes.

There are strong reasons for doubting whether maturation of reticulocytes in the circulating blood of man or animals occurs at an appreciable rate. The observation that rats with anemia due to deficiency in iron have reticulocytic showers (up to 1,000,000 per cubic millimeter) for two weeks when given copper alone, without a rise in the red count during this period, speaks against the classic 50 per cent maturation each twenty-four hours.<sup>6</sup> In the experiments of Morris and others on the injection of gastric juice in man, they noted prolonged high reticu-

TABLE 3—*Fall in Nonreticulocytic Cells During the Reticulocytic Shower*\*

Observer	Day of Therapy	Nonreticulocytic Red Blood Cells, Millions	Reticulocytic Red Blood Cells, Millions	Actual Loss of Nonreticulocytic Cells, Millions	Calculated Loss of Nonreticulocytic Cells, Millions in 24 Hours
Minot, Murphy and Stetson M Sc 175 581, 1928	3	1.0			
	7		(27%)		
	8	0.9	0.5	0.1	0.25
Riddle and Sturgis Am J M Sc 180 1, 1930	0	0.69			
	4	0.50	(30%) 0.62	0.12	0.35
Goldhamer, Isaacs and Sturgis Am J M Sc 186 84, 1933	2	1.36	0.23		
	3	1.44	0.56	0.12	0.23
	4	1.02	0.85	0.42	0.70
Goldhamer, Isaacs and Sturgis Am J M Sc 186 84, 1933	2	0.93	0.10		
	3	0.80	0.36	0.13	0.18
	4	0.68	0.55	0.12	0.30
	5	0.64	0.61	0.04	0.31

\* Based on data published by various observers. The "calculated" daily loss of nonreticulated cells is based on the assumption that 50 per cent of the reticulocytes mature every twenty-four hours.

locytosis, with no significant rise in the red cell count until after the reticulocyte count began to fall. Even in older experiments with liver, it was apparent that the greater the reticulocytosis, the less the concomitant rise in the red count, although a rapid rise in the red count occurred later. The steep rise in the red count occurs here, as with injections of gastric juice, only after the reticulocyte count begins to fall. During the rise in reticulocytes, the count of nonreticulated cells actually falls in cases in which the reticulocytosis is sharp and marked (table 3). Since the excretion rate of bile pigment also falls rapidly when the reticulocytic peak is reached,<sup>7</sup> it seems unlikely that hemolysis

6 Elvehjem, C. A., and Schultz, M. O. The Relation of Iron and Copper to Reticulocyte Response in Anemic Rats, *J Biol Chem* **102** 357 (Oct) 1933.

7 Farquharson, R. F., Borsook, H., and Goulding, A. M. Pigment Metabolism and Destruction of Blood in Addison's (Pernicious) Anemia, *Arch Int Med* **48** 1156 (Dec) 1931.



is occurring at the rate required by the theory that 50 per cent or more reticulocytes are maturing and being hemolyzed each day. These clinical data, with our observations on the fragility of reticulocytes, suggest that they rarely mature in the circulating blood, but have a short period of survival. Recovery from anemias of various sorts is accompanied or preceded by a brief shower of reticulocytes, but recovery occurs in spite of this premature launching of fragile and short-lived cells, not because of it.

#### CONCLUSIONS

The reticulocytes, and particularly the young (heavily stained) ones, are more easily destroyed in shed blood and in the circulating whole blood by saponin (and by citrate and oxalate in whole shed blood) than are the other red cells.

The maturation of reticulocytes in the circulating blood is not proved, it seems not to occur on any significant scale.

The occurrence of a reticulocytic crisis early in the treatment of anemia is probably an unavoidable evil associated with a change in the structure and function of the bone marrow. This precedes and delays the rise in the red cell count.

# TULAREMIA

A CONSIDERATION OF ONE HUNDRED AND TWENTY-THREE CASES,  
WITH OBSERVATIONS AT AUTOPSY IN ONE

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It is my purpose in this paper not to review to any extent the literature pertaining to tularemia but to report a study of 123 cases of tularemia coming under my personal observation and, incidentally, to add new clinical and pathologic material to the known facts concerning an interesting and comparatively new disease

## HISTORY

Tularemia has the distinction of being a truly American disease. American investigators not only discovered its specific etiologic agent and its modes of transmission from animal to animal and from animal to man but described completely, for the first time, its bacteriology, pathology and clinical manifestations.

McCoy,<sup>1</sup> in 1911, contributed the first scientific knowledge of the disease by his description of a "plague-like disease of rodents" which he encountered while investigating a plague among ground squirrels in California. In 1912, the causative organism was identified by McCoy and Chapin<sup>2</sup> and given the name *Bacillus tularensis*, after the county of Tulare, Calif., in which its discovery was made. During this same year, Chapin<sup>3</sup> demonstrated for the first time agglutinins of the organism in his own blood and in that of a laboratory attendant. They had just recovered from a febrile illness which, in the light of present knowledge, is recognized to have been tularemia. In 1914, Vail<sup>4</sup> and

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The material used in this article was presented as a part of the Scientific Exhibit at the Seventy-Ninth Annual Session of the American Medical Association at Philadelphia in June 1931, and at the Eighty-First Annual Session of the Medical Society of the State of Pennsylvania at Scranton, October 1931.

1 McCoy, G. W. A Plague-Like Disease of Rodents, *Pub Health Bull* 43 53, 1911.

2 McCoy, G. W., and Chapin, C. W. Bacterium *Tularensis* the Cause of a Plague-Like Disease of Rodents, *U. S. Pub Health & Mar Hosp Bull* 53, 1912, p. 21.

3 McCoy, G. W., and Chapin, C. W. Further Observations on a Plague-Like Disease of Rodents with a Preliminary Note on the Causative Agent, *Bacterium Tularensis*, *J Infect Dis* 10 61, 1912.

4 Vail, D. T. *Bacillus Tularensis* Infection of the Eye, *Ophth Rec* 23 487, 1914.

Wherry and Lamb<sup>5</sup> of Cincinnati reported the first case in a human being to receive bacteriologic confirmation by the isolation of the organism. Wherry<sup>6</sup> also isolated the organism from a wild cottontail rabbit found dead. Under the title "A New Bacterial Disease of Rodents Transmissible to Man," Wherry<sup>7</sup> first called attention to its infectivity for man. Francis,<sup>8</sup> in 1919 and 1920, working in Utah recognized the identity of "deer fly fever" and "plague-like disease of rodents" and named the disease tularemia because of the prevalence in the blood of *Bacterium tularense*. With Mayne<sup>9</sup> he demonstrated the agency of *Chrysops discalis* in transmission. His article entitled "Tularemia Francis 1921. A New Disease of Man"<sup>10</sup> is one of the really great classics of medical literature. In 1925, Novy unearthed a letter written in 1907 by Ancil Martin, an ophthalmic surgeon in Arizona, in which he called attention to 5 cases in human beings occurring in his practice. Francis' article also focused attention on an article written in 1911 by Pearse,<sup>11</sup> in which he described clinically, under the title "Insect Bites," 7 cases in human beings which he observed in Utah, where the disease became popularly known as "deer fly fever." Ohara,<sup>12</sup> in 1925, reported a fatal disease of wild rabbits in Japan which was proved by Francis and Moore<sup>13</sup> to be tularemia. In 1928, Russian workers<sup>14</sup> reported a series of cases

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5 Wherry, W. B., and Lamb, B. H. Infection of Man with *Bacterium Tularense*, *J Infect Dis* **15** 331, 1914.

6 Wherry, W. B., and Lamb, B. H. Discovery of *Bacterium Tularense* in Wild Rabbits, and the Danger of Its Transfer to Man, *J A M A* **63** 2041 (Dec 5) 1914.

7 Wherry, W. B. A New Bacterial Disease of Rodents Transmissible to Man, *Pub Health Rep* **29** 3387, 1914.

8 Francis, E. Occurrence of Tularemia in Nature as a Disease of Man, *Pub Health Rep* **36** 1731, 1921.

9 Francis, E., and Mayne, B. Experimental Transmission of Tularemia by Flies of the Species *Chrysops Discalis*, *Pub Health Rep* **36** 1738, 1921.

10 Francis, E. Tularemia Francis 1921. A New Disease of Man, *J A M A* **78** 1015 (April 8) 1922.

11 Pearse, R. A. Insect Bites, *Northwest Med* **3** 81 (March) 1911.

12 Ohara, H. Concerning an Acute Febrile Disease Transmitted by Wild Rabbits. A Preliminary Report, *Jikken Iho* March 12, 1925 (Japanese text).

13 Francis, E., and Moore, D. Identity of Ohara's Disease and Tularemia, *J A M A* **86** 1329 (May 1) 1926.

14 Golov, D. A., Kniazevsky, A. N., Berdnikov, V. A., and Tiflov, V. E. Plague-Like Infections (*Tularemia?*) in the Region of the Basin of the Oural in the Spring of 1928, *Rev de microbiol, d'epidemiol et parasitol* **7** 301, 1928. Nikanorov, S. M. Tularemia in North America and Tularemia-Like Disease in U. S. S. R., *ibid* **7** 289, 1928. Suvorov, S. V., Wolferz, A. A., and Voronkova, M. M. Plague-Like Lymphadenitis in the Rayon of Astrakhan, *ibid* **7** 293, 1928. Wolferz, A. A. Tularemia-Like Disease on the Banks of the Oka in 1928, *ibid* **7** 299, 1928.

contracted from handling the European water vole. In 1929, McNabb<sup>15</sup> reported the first case appearing in Canada. It was first recognized in Norway<sup>16</sup> in 1930, and in Sweden<sup>17</sup> in 1932. Laboratory workers have acquired the disease in England.

It is interesting that tularemia was known to have existed in rabbits in Kentucky prior to 1910 and that the disease occurred in man as early as 1907. My father, a practicing physician, advised me as early as 1910 not to hunt rabbits because of a fatal epizootic among them at that time. He also reported that there had been similar plagues occurring in rabbits at intervals over a period of twenty years and that he considered the disease contagious to man.

As early as 1907, Dr. Cowley of Berea, Ky., observed 2 cases of typical tularemia contracted by members of a family by handling the same rabbit. Agglutination of *Bact. tularensis* in these cases is in dilutions of 1:120 at the present time.

#### ETIOLOGY

*Distribution and Incidence*—Tularemia is a widespread disease, endemic in most communities and at certain seasons epidemic. The natural distribution of the disease in the United States is that of its carriers, the wood ticks *Deimacentor Andersoni* Stiles, *Deimacentor variabilis* and *Deimacentor occidentalis* Newmann. Shipment of infected rabbits was the cause of the disease in certain states. Cases in human beings were reported from forty-three states of the United States and from the District of Columbia. The disease was described in Japan in 1925, in Russia in 1928, in Norway in 1929, in Canada in 1929 and in Sweden in 1932.

Although cases of natural infection in human beings occur in every month of the year, the seasonal prevalence of ticks (from March to August) and of flies (from June to September) and the game laws protecting rabbits tend to control the seasonal incidence of the disease. The incidence of the disease in Kentucky is almost entirely controlled by epizootics in cottontail rabbits, which occur cyclically, at irregular intervals and under conditions as yet imperfectly known. The explanation of the interepidemic periods is not altogether satisfactory because sporadic cases occur then.

*Sex, Race and Age*—Men and women are equally susceptible to the disease. Among the patients considered in this study there were 69

15 McNabb, A. L. Tularemia. First Case Reported in Canada, *Canad. Pub. Health J.* **21**: 91, 1930.

16 Thjøtta, Theodore. Three Cases of Tularemia. A Disease Hitherto Not Diagnosed in Norway, *Norsk mag. f. lægevidensk.* **91**: 224, 1930, *Tularemia og dens forekomst i Norge*, Særtryk f. nord. med. tidskr. **2**: 177, 1930.

17 Granstrom, K. O. Tularemia Oculoglandularis, *Acta ophth.* **10**: 237, 1932.

males and 54 females Race did not play an important rôle, 14 cases were observed in Negroes

*Immunity*—Not all persons exposed to infection contract the disease The long persistence of agglutinins in the blood of patients who have recovered may be an indication of their immunity No instance of a second attack has been recorded

*Contagion*—Surgeons who have incised or excised suppurating glands have not contracted the infection Members of patients' families, whose aseptic technic was nil, have dressed primary lesions and suppurating nodules and glands innumerable times without contracting the disease Harris<sup>18</sup> reported a case in which a mother is thought to have acquired the disease as a result of picking her thumb while dressing the tularemic ulcer of her son, who had been bitten by an infected deer fly There is a possibility that in a case of my knowledge the infection was transmitted by the bite of a fly which had previously had access to pus from suppurating glands of an infected human being

*Distribution in the Body*—That an early bacteremia exists in man is made manifest not only by the occurrence of typical foci of necrosis in the spleen, liver and lungs but by the recovery of the organism from the blood as early as the third day and as late as the twelfth day of the illness The organism has not been recovered from the blood after the twelfth day During life, cultures have been obtained from pleural effusion, ascitic fluid, sputum, lymph glands, primary ulcers and spinal fluid At autopsy, the organism is found widely distributed, in greatest number and most constantly in the regional lymph glands (axillary, cervical and submaxillary), lungs, liver, spleen and blood

*Bacteriology*—*Bact tularensis* is a small pleomorphic organism, gram-negative, nonmotile and nonspore-bearing It grows under aerobic conditions The optimum temperature is 37 C, and the optimum  $p_H$  range, between 6.8 and 7.3 It causes fermentation in mediums containing dextrose, levulose, mannose and glycerin, forming acid but not gas It grows well on coagulated egg yolk and blood dextrose cystine agar, but not on ordinary laboratory mediums Bacillary, coccoid and bipolar forms are noted In smears it stains well with crystal violet or aniline gentian violet, and in sections of animal tissue it stains best with Giemsa's solution Foshay and his co-workers<sup>19</sup> demonstrated the presence of the organism in sections of human tissue from 2 fatal cases of tularemia A temperature of from 56 to 58 C kills the organism in cultures and in spleen tissue in ten minutes Cultures suspended in saline

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18 Harris, C. E. Tularemia, *M. Sentinel* **32** 6, 1924

19 Fougler, M., Glazer, A. M., and Foshay, L. Tularemia. Report of Case with Postmortem Observations and Note on Staining of *Bacterium Tularensis* in Tissue Section, *J. A. M. A.* **98** 951 (March 19) 1932

solution containing 0.1 per cent of a dilute solution of formaldehyde, U. S. P. (37 per cent) are rendered nonvirulent after twenty-four hours. Spleen tissue rubbed in 1 per cent cresol is free from virulence after two minutes. Pure, undiluted glycerin into which cultures or spleen tissue is placed preserves the virulence for one month at room temperature, for six months at 10 C and for one year at  $-14^{\circ}\text{C}$ . Treatment with glycerin in conjunction with annual or semiannual animal passage serves to perpetuate the virulence of a strain for years. Spleen tissue frozen at less than  $-14^{\circ}\text{C}$  loses its virulence in one month. Prolonged refrigeration of cultures on a medium of coagulated egg yolk greatly reduces their virulence for certain laboratory animals.

Frozen rabbits are infective for three but not for four weeks. The virus resists drying in bedbug feces for twenty-six days.

For its propagation in nature, *Bact. tularensis*, as far as is known, depends entirely on the wood ticks *Dermacentor Andersoni* Stiles, *Dermacentor variabilis* and *Dermacentor occidentalis* Newmann, which bite both rabbits and man. The hereditary transmission of the organism by female wood ticks to their eggs, larvae and nymphs establishes this host as a permanent reservoir of infection.

Other blood-sucking insects—lice, flies and ticks—are believed to transmit the infection from animal to animal in nature.

#### MORBID ANATOMY

While the individual lesions grossly and histologically simulate those of tuberculosis, the pathologic process as a whole has a certain distinctiveness.

Focal areas of necrosis in various stages of evolution are the essential lesions in the body tissues. Following the primary insult there is a cellular reaction consisting of polymorphonuclear leukocytes and epithelioid cells, often enmeshed in fibrin. As the lesion advances necrosis occurs in the center, and a marginal zone of epithelioid and fibroblastic granulation tissue in radial arrangement appears. In older lesions, this is further surrounded by a peripheral zone of lymphocytes with cells of the Langerhans type.

#### REPORT OF A CASE

The characteristic pathologic anatomy can best be described by presenting the observations in a fatal case of the primary ophthalmic type of the disease coming to autopsy on the twelfth day of the illness.<sup>20</sup>

*Macroscopic Examination*—The body was that of a well developed and well nourished Negro about 40 years of age.

*Eyes*—The lids of the right eye were moderately edematous. The palpebral conjunctiva was diffusely covered by a thick, grayish-yellow, fibrinopurulent mem-

<sup>20</sup> Autopsy was performed by Dr. E. S. Maxwell, Department of Pathology, the Lexington Clinic.

brane measuring from 1 to 2 mm in thickness. This membrane also extended over the bulbar conjunctiva to the cornea, where it stopped abruptly. The surface of the membrane was rather irregular, but no definite ulcers were recognized. Considerable material was easily scraped from the surface, but the membrane was closely adherent to the deeper structures. The iris, lens, vitreous and retina were apparently normal. The left eye showed no gross lesions.

**Glands** The preauricular, superior cervical and submaxillary glands on the right side were enlarged. The glands of the hilus of each lung, as well as the mediastinal glands, were moderately enlarged. The mesenteric and retroperitoneal glands were moderately enlarged, measuring from 5 to 10 mm in diameter.

**Thorax** The viscera of the thoracic and abdominal cavities were completely transposed.

**Lungs** The lungs were bound down posteriorly by numerous fibrinous and fibrous adhesions between the visceral and the parietal pleura. Many small petechial hemorrhages were scattered over the pleural surfaces, particularly on the diaphragmatic surface and between the lobes. The right pleura presented a thin, delicate, fibrinopurulent membrane over the dependent portion. Diffusely scattered throughout both lungs were numerous small, discrete, miliary and confluent tubercles varying from 1 to 10 cm in diameter. On section, the larger areas were gray and presented softened centers. Both lungs showed moderate edema in the dependent portions.

**Cardiovascular System** The pericardium was smooth, and the cavity contained no excess fluid. The heart, except for a complete transposition of all anatomic structures, showed no unusual features.

**Peritoneum** The peritoneum was covered by a thin, delicate, fibrinopurulent exudate, and a small excess of turbid fluid was present in the cavity. The peritoneal coat of the appendix presented more exudate than the peritoneum in general.

**Liver** The liver was slightly larger than normal and the surface of the cut section was rather cloudy. A moderate number of small grayish-yellow lesions, averaging about 1 mm in diameter, were seen beneath the capsule and on the cut section. An occasional larger confluent mass of grayish tissue was found. The gallbladder presented no abnormalities.

**Spleen** The spleen was not enlarged, weighing 110 Gm. The capsule was thickened and was covered by a thin fibrinopurulent exudate. The surface of the cut section showed numerous minute yellowish opaque spots with cleancut margins.

**Kidney** The left kidney was approximately normal in size. No changes were seen in the capsule. The capsule stripped readily. The surface of the cut section showed a definite cloudiness in the cortex. The lining of the pelvis was smooth. The ureter was grossly normal. The right kidney and ureter were similar to the left. The pancreas showed no gross lesions. The suprarenal glands were grossly normal.

**Other Organs** The mucosa of the stomach and of the small and large intestines did not show evidence of disease. The bladder, prostate gland and testicles showed no gross lesions.

**Histopathologic Examination**—**Glands** The preauricular and cervical lymph nodes showed miliary and confluent areas of caseous necrosis surrounded by a zone of endothelial cells containing many foreign body giant cells. The submaxillary salivary gland tissue showed no distinctive pathologic condition. The lymph nodes of the hilus of each lung and of the mediastinal, mesenteric and retroperitoneal tissues showed areas similar to those noted in the preauricular and cervical glands.

**Eyes** The conjunctiva and cornea were covered with a heavy layer of lymphocytic and polymorphonuclear infiltration surrounding multiple foci of early caseous necrosis. The inflammatory exudate and foci of necrosis entirely replaced the squamous epithelium. The ciliary body, choroid and retina were not involved.

**Lungs** Sections from the small nodules in the lungs showed areas of acute caseous necrosis with complete destruction of the alveolar walls. Many of these areas of necrosis were not associated with the bronchi or bronchioles. There were acute passive congestion and edema. The pleura was covered with a fibrinopurulent exudate, on the surface of which was a layer in which the nuclei of all cells were degenerated.

**Liver** The liver showed numerous areas of milium focal necrosis. The smaller areas involved only a few liver cells, while the larger ones involved several lobules. The larger foci had caseous centers. A thin area of fibrinous exudate was found on the peritoneal surface of the liver. The liver cells showed moderate cloudy swelling.

**Spleen** In the splenic parenchyma were many areas of acute caseous necrosis, many of which were confluent and formed large lesions. The capsule was covered with a thin layer of fibrinopurulent exudate.

**Peritoneum** The peritoneum showed an infiltration of lymphoid cells with decided pyknosis and degenerative changes in the cells of the outer portion.

**Kidneys** The kidneys showed slight degenerative changes in the epithelium of the convoluted tubules. The glomeruli were intact.

**Other Organs** The suprarenal glands, pancreas, testicles, prostate gland and bladder showed no abnormalities.

#### TYPES OF INFECTION

The classification preferred and used entirely in this report is as follows:

1 Primary cutaneous tularemia (ulceroglandular and glandular tularemia), in which the primary lesion is a papule of the skin, later an ulcer, and is accompanied by enlargement of the regional lymph glands. In rare instances the primary lesion is absent at the site of infection but there is enlargement of the regional lymph glands. Ohara<sup>21</sup> proved by inoculation of a human being that this can occur.

2 Primary ophthalmic tularemia (oculoglandular tularemia), in which the primary lesion is a conjunctivitis and is accompanied by enlargement of the regional lymph glands.

3 Cryptogenetic tularemia (typhoid type), in which *Bact. tularensis* enters the body without causing any cutaneous lesion or local manifestation. This is the type usually presented by laboratory workers.

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<sup>21</sup> Ohara, H. Human Inoculation Experiment with a Disease of Wild Rabbits with a Bacteriological Study, *Kinsei Igaku*, vol 12, no 5, 1926 (Japanese text).



## SOURCES OF HUMAN INFECTION

There are many ways by which the disease may be transmitted from an infected host to man. While wild rabbits and wood ticks (*Deimacentor Andersoni* Stiles) constitute the important reservoirs of infection



Fig 1—Bilateral primary ophthalmic tularemia with regional adenopathy and subcutaneous nodule, four weeks after onset

for other animals and man, other animal hosts and transmitters (the woodchuck, opossum, muskrat, skunk, European water vole, cat, coyote, quail, sheep, hog, gray and red squirrel, ground squirrel and European marmot, insect vectors, such as the deer fly [*Chrysops discalis*] and ticks

[*Dermacontor variabilis*, *Dermacontor occidentalis* Newmann]) have been sources of infection in various localities

In this series of cases the sources of infection were as follows

1 For primary cutaneous tularemia with regional glandular enlargement (102 cases) One patient had associated with sheep and ticks One had been bitten by a fly (*Stomoxys calcitrans*) Ninety-two had handled or dressed wild rabbits One had been bitten by an opossum One had skinned an opossum One had skinned a red squirrel Two had been bitten by a cat One had had an open wound licked by a cat One had crushed rabbit lice on his hand One had picked ticks from a dog

2 For primary cutaneous tularemia without a primary lesion but with regional glandular enlargement (6 cases) All the patients had dressed wild rabbits

3 For primary ophthalmic tularemia (6 cases) All the patients had dressed wild rabbits

4 For cryptogenetic tularemia with no initial lesion, regional glandular involvement or local manifestations (9 cases) One patient had picked ticks from a dog All the others had skinned and dressed wild rabbits

#### MULTIPLE INFECTION

Three members of one family contracted tularemia of the primary cutaneous type by handling the same rabbit Double infections occurred in 13 instances the primary cutaneous type occurring in both members of the family in 7 instances, the primary cutaneous type in one member and the cryptogenetic type in the other, in 4 instances, and the primary cutaneous type in one member and regional glandular involvement without a primary lesion in the other, in 2 instances

#### PERIOD OF INCUBATION

The average period of incubation, definitely determined in 58 cases in which there was a single exposure to infection, was four and one-half days The incubation period could not be determined in all cases

#### SYMPTOMS AND GENERAL COURSE

Although extraordinarily variable in its local manifestations, the mode of onset and the general constitutional reaction in the various types of tularemia are identical Complications at the onset or during the course of the disease may alter the general characters

The constitutional disturbance in cases of mild tularemia is slight, and there are instances of extensive local disease without grave systemic symptoms More commonly, the onset is sudden, often occurring while

the patient is at work, and is manifested characteristically by headache, vomiting, chilliness, chills, aching bodily pains, sweating, prostration and fever.

During the active stage, which lasts from two to three weeks, fever, weakness and prostration, chilliness, recurring chills and sweats, aching pains in the back and extremities and loss of weight are the usual symptoms. Delirium and stupor may be present in the more severe cases. Following the onset of the primary cutaneous type of the disease, the patient may note that a previous cut or sore is acutely inflamed and painful or that a small, raised, red papule makes its appearance where hitherto there was no cut or abrasion. Within from thirty-

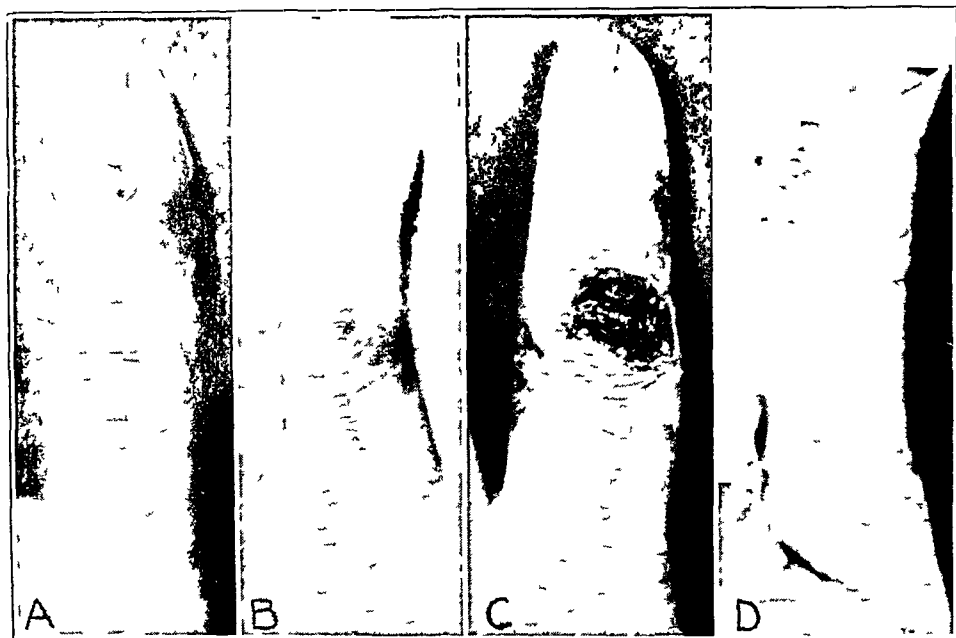


Fig 2—Primary cutaneous lesions of tularemia. *A*, a primary papule on the seventh day, *B*, a primary papule showing beginning liberation of the necrotic core on the fourteenth day, *C*, a primary ulcer after liberation of the necrotic core on the twenty-first day, *D*, a primary ulcer on the forty-second day.

six to forty-eight hours after the onset, the regional lymph glands may be slightly enlarged and tender. Pain is complained of in this region frequently before attention is called to the primary lesion. Painful red streaks may be seen extending from the primary lesions toward the regional glands, or vice versa.

In cases in which a regional adenopathy occurs without a primary lesion, the constitutional reaction and course are the same.

In the cryptogenetic type, the onset, course, constitutional symptoms and duration of the disease are the same as in the other types.

In the ophthalmic type, the primary localization is in the conjunctival sac. It occurred bilaterally in 1 of the 6 cases observed. The early sub-

jective local symptoms are itching, swelling of the lids (accompanied by lachrimation), photophobia and pain. Almost simultaneously the preauricular, parotid, submaxillary and cervical glands become swollen, tender and painful. In severe cases, the axillary glands may be involved. If the patient is seen shortly after the onset, the conjunctiva presents the picture of acute conjunctivitis, chemosis is pronounced and the conjunctiva is a vivid scarlet. The lids are decidedly swollen. Small, discrete, yellow nodules (measuring from 1 to 6 mm in diameter) appear soon on the chemotic conjunctiva of both lids. Rarely, single nodules appear on the bulbar conjunctiva, which at this time is edematous and injected. In 2 cases, the palpebral and bulbar conjunctivae were covered by a gray, translucent, organized exudate which ended abruptly at the cornea. In 1 case

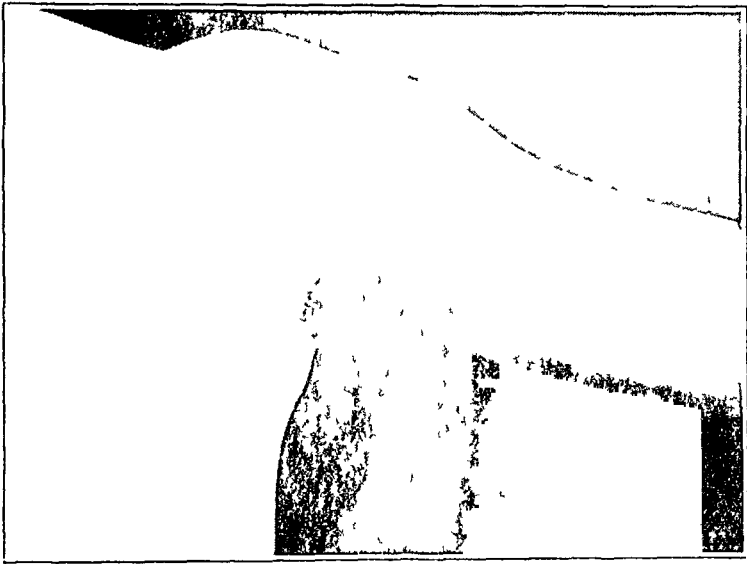


Fig. 3—Suppurating adenopathy four weeks after onset

in which there was bilateral ocular involvement the conjunctivitis was equally severe in the two eyes, but nodules did not appear in the conjunctiva of one eye, and the inflammatory reaction subsided much more rapidly. The regional adenopathy in this case was unilateral. In another case, no nodules or definite ulcers were noted, but there seemed to be an irregular pitting in the inflamed conjunctiva. The small necrotic nodules tend to break down, leaving small punched-out ulcers which eventually heal without leaving a scar. There is a mucowatery or mucopurulent discharge, usually straw-colored, which is at first moderately profuse and lessens in amount as the local condition improves. The active conjunctivitis continues from three to five weeks, then the swelling gradually recedes. A solitary subcutaneous nodule was present on the cheek in 1 case. The glands may remain small and nodular or become greatly enlarged, the enlargement persisting for many months or

progress to suppuration. Suppuration occurred in 5 of the 6 cases of primary ophthalmic tularemia. A papular eruption appeared on the same side of the face and neck during the first week of the disease in 1 case.

#### SPECIAL FEATURES

*Pulmonic Tularemia*—Pulmonic tularemia is another manifestation of the hematogenous dissemination of the disease. A review of the autopsy observations in cases of death from tularemia is significant. Invariably the essential pulmonic lesion is tularemic focal necrosis surrounded more or less by a zone of lobular pneumonia. *Bact tularensis* has been repeatedly isolated from these lesions. The character of the invading organism is responsible for this pathologic condition. In 1928, Bunker and Smith<sup>22</sup> isolated *Bact tularensis* from the sputum during the twelfth day of the illness and from the lungs and other tissues at autopsy. During the same year, I<sup>23</sup> called attention for the first time to a case of primary pulmonic tularemia. Sixteen cases in this series presented distinct pulmonary involvement characteristic of the variable clinical findings noted in bronchopneumonia. Nine cases occurred in association with the primary cutaneous type of the disease. In 7 cases the symptoms were primarily pulmonic (cryptogenetic type), beginning abruptly with fever, dyspnea, cough and sometimes pain in the chest. In 4 of these cases, one other member of the family had the primary cutaneous type of the disease from handling the same rabbit. Death occurred in 4 cases, indicating a mortality of 25 per cent in pulmonic tularemia.

Pulmonic symptoms may usher in the onset or appear some time during the course of the disease. More often, the usual symptoms of onset of pulmonic tularemia are increase in the fever and pulse rate, severe cough and shortness of breath. Pleurisy with effusion was observed at the onset in 3 cases. During the course of the disease, a distressing cough, increasing dyspnea and cyanosis are important clinical features. Delirium and stupor may occur in the more severe cases.

As a rule, both lungs are affected, but the clinical signs generally are more extensive in one lung than in the other. Physical signs may vary from day to day, suggestive signs disappearing and reappearing later or being replaced by fresh signs in other locations. The physical signs may at first be those of capillary bronchitis, as indicated by the presence of fine crepitant and sibilant râles and the absence of dullness to percussion. After a few days medium moist, sticky râles may appear over the lower lobes posteriorly, and one can recognize areas of

22 Bunker, C W O, and Smith, E E. Tularemia. Report of Four Cases One Fatal, with Autopsy Report, U S Nav M Bull **26** 901, 1928.

23 Kavanaugh, C N, in discussion on Francis<sup>24</sup>

impaired resonance in haphazard patches or, when the patches of bronchopneumonia have merged, actual dullness. The breath sounds may be harsh, but they are not definitely tubular. If numerous foci involve the greater part of a lobe the breathing may be tubular and may be mistaken for that of lobar pneumonia. The sputum is usually scanty and tenacious but seldom bloody or rusty. The course is variable, the disease may be fulminant, the patient dying in from four to twelve days, or it may persist after the febrile course of the disease. The areas of consolidation clear up slowly and often remain for a long time after the constitutional symptoms have disappeared.

*Primary Cutaneous Lesion*—A primary lesion occurred on the finger or hand in 102 cases. It was single in 87 cases and multiple in 15 and

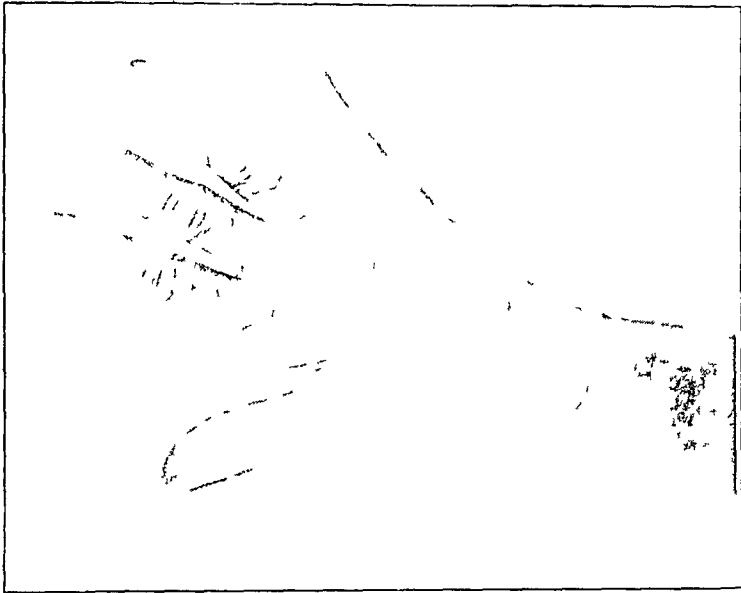


Fig. 4—A solitary subcutaneous nodule and multiple primary lesions on the fingers

occurred bilaterally in 11. The largest number of primary lesions in any case was five. Neither its multiple nor its bilateral occurrence seemed to have any effect on the degree of severity of the other symptoms. The initial lesion appears within from three to seven days after inoculation, and it first manifests itself as a small, painful, inflamed papule which gradually enlarges and on breaking down liberates a necrotic core, leaving an ulcer with raised edges and a punched-out appearance which has a grayish-red necrotic base which is exquisitely sensitive. The size attained is variable, and when small the sore may be overlooked, particularly if the patient is not seen early in the course of the disease. Ulcers on the dorsum of the hand are usually more shallow than those on the palmar surface where the skin is thicker. It must be emphasized that the infection may occur without any decided primary lesion or with only a superficial erosion or ulceration. Absence of a

history of an initial lesion is of no value in excluding the possibility of infection. The size of the ulcer is decidedly increased following surgical incision, and an exacerbation of general symptoms follows each incision. The discharge is scanty and serous. The ulcer heals slowly and is replaced by scar tissue. Incision of the primary lesion materially lengthens the time required for its healing.

*Subcutaneous Nodules*—Subcutaneous nodules occurred in 28 instances. They were found on either the anterior or the posterior surface of the forearm or arm, and occasionally they extended from the primary lesion to the enlarged axillary glands. In 1 case of the primary ophthalmic type, a single nodule was noted on the cheek. These nodules are at first firm and movable, later they frequently become attached to the skin, and many of them ultimately suppurate. In the cases in this series they varied in size from that of a pea to 1 cm in diameter, and their number varied from one to thirty. In several instances con-



Fig 5—Multiple subcutaneous nodules on the hand and arm

glomerate masses of nodules (nodular lymphangitis) 10 cm long by 3 cm wide were observed. Pain was noted only in the cases in which suppuration occurred.

*Glandular Involvement*—In a small percentage of the cases lymph glands other than the regional glands were slightly enlarged and tender. In 3 cases in which the axillary glands were primarily involved the submaxillary glands on the same side were visibly enlarged. Unilateral enlargement of the axillary glands was noted in 1 case of the ophthalmic type. Enlargement of the epitrochlear glands associated with axillary adenopathy was noted in several cases. In 33 cases (29.5 per cent) the glands suppurated and after the inflammation had subsided either were incised or ruptured through a soft, thin, bluish-red spot in the skin. In the rest of the cases the glands did not break down but remained hard, palpable and rather tender for from three to twelve months, gradually returning to normal. Suppuration of lymph glands was noted four and even twenty-four months after the disease.

Suppuration of regional glands was not necessarily accompanied by suppuration of nodules, but in all cases in which there was suppuration of nodules the regional glands also broke down

*Cervical Adenitis*—Four cases presented a unilateral enlargement of the cervical glands without a primary lesion or other local manifestations. In 2 of these cases one other member of the family was suffering from primary cutaneous tularemia, the primary lesion having been contracted from handling the same rabbit. The glands were suppurative in 2 of the 4 cases. No lesions were noted in the mouth or throat.

*Cutaneous Eruption*—A cutaneous eruption was observed in 23 cases (18.7 per cent). It usually appeared during the second or third week

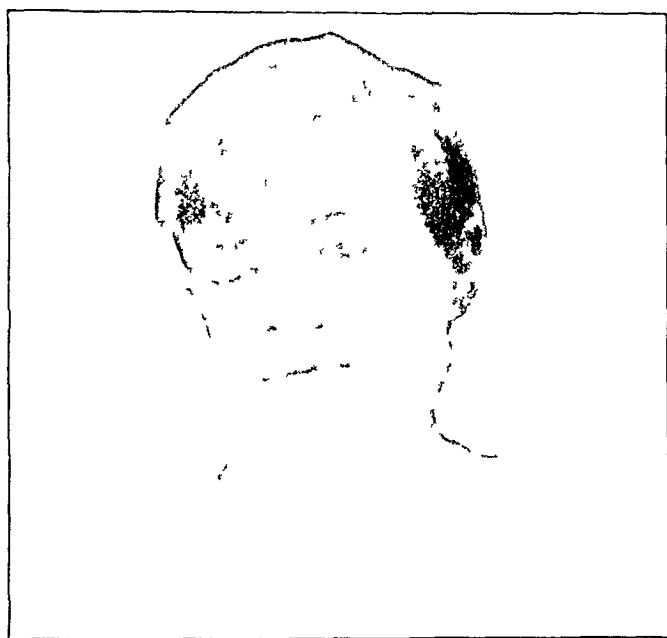


Fig. 6—Left primary ophthalmic tularemia with regional adenopathy and complicating dacrocystitis

and lasted from a few days to three or four weeks. It occurred most frequently on the arms and neck, was always bilateral and in most instances was symmetrically distributed.

The polymorphism of the eruption is so marked that it is practically impossible to designate a characteristic lesion, the eruption being macular, papular, vesicular or pustular or any transitional form from one of these types to another. Evolution was seldom complete in these lesions. Involution was usually by absorption or exfoliation.

The essential characteristics, along with a bacteremia, suggest that such eruptions are the result of toxins in the circulation or of local invasion of bacteria.

In 2 cases lesions typical of erythema nodosum were noted on the shins and thighs. Herpes was noted on the buccal mucous membrane in several cases.



In a double infection from the same rabbit, two contrasting types of eruption were noted in one case a papular type which terminated in absorption, in the other, a maculopapular eruption which terminated in a brawny desquamation. In 3 cases during the course of the disease, a pronounced acne developed on the back and shoulders. No scarring or pigmentation was noted after the disappearance of the eruption in any case.

*Changes in the Blood*—Secondary anemia is common, with a red cell count of between 3,500,000 and 4,000,000 and a hemoglobin content of 70 per cent. The blood smear shows achromia of red cells. Early in the disease a leukopenia (white cell count from 5,000 to 7,000) is common but sometimes the count is higher frequently normal. A polymorphonuclear leukocytosis of from slight to moderate degree (from 12,000 to 15,000 cells) may occur during the course of the disease.

*Fever*—The temperature records were not particularly characteristic in the few cases in which complete charts were available. Continuous high temperature was noted in cases with extreme toxemia. Francis,<sup>24</sup> viewing 11 complete temperature charts for cases of the cryptogenetic type of the disease, was struck by the constancy of the sequence of initial rise remission and secondary rise. The whole febrile course usually lasts from two to three weeks. Recurring mild attacks of fever were noted as late as ten months after the disease.

*Splenomegaly*—Splenomegaly occurred in approximately 20 per cent of the cases. The enlargement, when evident, is not great, as a rule, a firm, tender edge is felt just below the left costal border. On rare occasions (5 cases) the spleen became large enough to extend three or four fingerbreadths below the costal margin. In these cases there was a subjective complaint of pain in this region and decided pain and tenderness were elicited on palpation (perisplenitis).

*Tularemia in Children*—Eight children with ages ranging from 6 to 12 years were observed. The mode of infection in these cases is of interest. One child killed a rabbit with his slingshot, 4 handled a rabbit which their dog had caught, 2 cleaned a rabbit that their dog had tied in a rock fence, and 1 caught an adult rabbit with his hands.

*Tularemia in Pregnancy*—Three patients contracted tularemia during pregnancy and were delivered of normal babies during the height of the infection. In 1 case labor was premature. The general course of the disease did not differ from its usual trend.

*Ambulatory Tularemia*—Although the onset may be severe a large percentage of patients are about and attend to their work throughout the whole attack.

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<sup>24</sup> Francis, E. Symptoms, Diagnosis and Pathology of Tularemia, J. A. M. A. **91** 1155 (Oct. 20) 1928.

## COMPLICATIONS

*Ocular Disturbances*—In only 1 case was there any permanent impairment of vision, an early papilledema was present which resulted in atrophy of the optic nerve and loss of vision in the involved eye. In a case reported by Magath and Yater<sup>25</sup> there were blindness of the affected eye following perforation of the cornea, protrusion of the iris and fusion of the cornea and iris into a compact mass.

A purulent dacryocystitis was noted in 1 case.

*Complications in the Breasts*—In 2 female patients a nodular lymphangitis extended from the axillary adenitis along the outer border of the pectoralis muscle and involved the breast. One of these patients was referred for amputation of the breast because of a suspected malignant condition. In each there was suppuration of the axillary glands and nodules of the breast necessitating wide incision and drainage.



Fig 7—Bilateral primary ophthalmic tularemia on the fifth day of the disease

*Thrombi in the Veins*—Thrombi occurred in only 1 instance. In this case both femoral veins were involved. The occurrence was manifested by a chill, pain and swelling along the veins, a rise in temperature and edema of the extremities. Recovery was complete.

*Pericarditis*—Pericarditis is extremely rare. Simpson<sup>26</sup> reported 1 case in which an effusion was present.

*Pleurisy*—Pleurisy occurred in 6 cases. In each instance it occurred with the onset. A pleural effusion was present in 3 cases.

*Pneumothorax*—Pneumothorax is rare. It occurred during convalescence in 1 case of the primary cutaneous type, presumably as a result of a ruptured focal abscess.

<sup>25</sup> Magath, T. B., and Yater, W. M. Three Cases of Tularemia, *M. Clin. North America* **10** 745, 1926.

<sup>26</sup> Simpson, V. E. Tularemia. A Consideration Based on a Resumé of the Literature and Personally Observed Cases, with a Report of an Unusual Complication, *Ann. Int. Med.* **2** 1092 (April) 1929.

*Abdominal Symptoms*—Abdominal pain and tenderness were noted in 5 cases and were present only at the onset. Operation for appendicitis was performed at the onset in 1 case of the primary cutaneous type because of iliac pain on the right side. The appendix was apparently normal. Parker and Spencer<sup>27</sup> observed these symptoms in several cases of the cryptogenetic type. In a case reported by Whiteis and Anthony<sup>28</sup> general abdominal pain was pronounced, and appendicitis as a complication was considered.

*Peritonitis*—One case of the primary ophthalmic type presented symptoms of general peritonitis. At autopsy there was a diffuse peritonitis. A case of tularemic peritonitis was reported by Fulmer and Kilbury<sup>29</sup> in which *Bact tularensis* was isolated from the ascitic fluid. Francis<sup>24</sup> reported a case with diarrhea and intestinal hemorrhages during the last ten days of illness. At autopsy there was general peritonitis with a plastic exudate covering the abdominal contents. Fulmer<sup>30</sup> reported a death occurring on the twelfth day with symptoms of general peritonitis.

*Disturbances of the Nervous System*—Delirium occurred in 6 cases, 4 of which terminated in death. In 2 of these cases the patients recovered in spite of advanced delirium and stupor during the course of the disease. During the first week of illness in 1 case an acute mania developed which persisted for several months. Recovery was complete. Hartman<sup>31</sup> reported his observations at autopsy in a case of acute tularemia with diffuse encephalitis. Bryant and Hirsch<sup>32</sup> recently reported a fatal case of tularemic leptomeningitis. Haizlip and O'Neil<sup>33</sup> reported a case of meningitis due to *Bact tularensis*, the organism being isolated from the spinal fluid.

*Disturbances of the Urinary System*—The urine is usually diminished at first and has the ordinary febrile characters.

*Osseous System*—Osteomyelitis of the femur occurred during convalescence in 1 case.

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27 Parker, R. R., and Spencer, R. R. Six Additional Cases of Laboratory Infection of Tularemia in Man, *Pub Health Rep* **41** 1341, 1926.

28 Whiteis, W. R., and Anthony, E. J. Tularemia in Iowa, *J Iowa M Soc* **16** 188, 1926.

29 Fulmer, S. C., and Kilbury, M. J. Tularemic Peritonitis, *J A M A* **89** 1661 (Nov 12) 1927.

30 Fulmer, S. C. Tularemia, *J Arkansas M Soc* **24** 61, 1927.

31 Hartman, F. W. Tularemic Encephalitis. Pathology of Acute Tularemia with Brain Involvement and Coexisting Tuberculosis, *Am J Path* **8** 57, 1932.

32 Bryant, A. R., and Hirsch, E. F. Tularemic Leptomeningitis. Report of Case, *Arch Path* **12** 917 (Dec) 1931.

Tularensis, *J A M A* **97** 704 (Sept 5) 1931.

33 Haizlip, J. O., and O'Neil, A. E. Case of Meningitis Due to Bacterium

## DIAGNOSIS

The most important factor in the diagnosis of tularemia is to have the disease in mind. In infections in human beings the fact that one has dressed or dissected wild rodents, especially wild rabbits or has been bitten by a tick or fly, with a primary cutaneous lesion or conjunctivitis with regional glandular involvement and characteristic onset symptoms suggests tularemia. In every doubtful case of fever the possibility of tularemia should be considered for this is the only outstanding symptom in the cryptogenetic type of the disease. A more difficult question to decide is whether an existing bronchopneumonia is simple or tularemic.

The intradermal test, suggested by Wherry<sup>34</sup> in 1917 and developed by Foshay<sup>35</sup> in 1932 is the earliest available diagnostic aid to determining the presence of tularemia. The reaction may become positive as early as the fourth day of the disease, practically a week before the

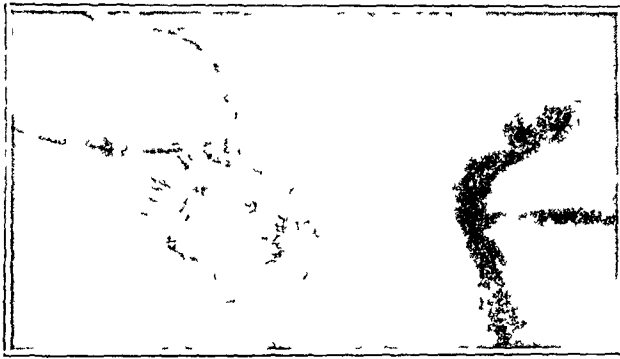


Fig. 8—A solitary nodule involving the ocular conjunctiva on the twentieth day after the onset

agglutinins usually appear in the blood. The test is specific and reliable, and the reaction becomes negative only when convalescence is complete.

The diagnosis can be confirmed further by obtaining an agglutination of *Bact. tularensis* by blood serum collected in the second week of illness and by noting an increase in the agglutination titer in serum collected a few days later or in the third week, or by isolation of *Bact. tularensis* from the guinea-pigs inoculated with material taken as early as the first week from the primary lesion or from the enlarged glands or the blood of the patient. The significance of a positive intradermal or agglutination test in the early diagnosis of tularemia is apparent, since it may be the only positive evidence of the disease. Microscopic examination of cover glass preparations taken direct from the patient is useless.

34 Wherry, quoted by Lamb, F. W. *Ophth. Rec.* **26** 221, 1917.

35 Foshay, L. Tularemia. Accurate and Earlier Diagnosis by Means of Intradermal Reaction, *J. Infect. Dis.* **51** 286, 1932.



Fig 9—Right primary ophthalmic tularemia with regional adenopathy on the tenth day after the onset



Fig 10—Annular patches on the neck with secondary crusting and scaling on the seventeenth day after the onset

*The Agglutination Test*—Specific agglutinins invariably appeared in all cases considered for this paper. The agglutinins are absent in the first week of the disease, they are always present at some time during the second week (1:10 to 1:160). In 2 cases agglutinins did not appear until the third week. During the third week there occurs an abrupt rise in the agglutinin titer, which reaches its maximum (1:1,280 or 1:2,560) from the fourth to the seventh week. The titer usually falls during the eighth week, gradually declining thereafter until at the end of the first year the average is about 1:160. Agglutinins have never entirely disappeared in any case, even from ten to twenty-four years after recovery.

*Cross-Agglutination*—The frequent cross-agglutination of *Bacterium abortus* and *Bacterium melitensis* by serums from known cases of *Bact. tularensis* infections, and the fact that serums from human patients with undulant fever may show cross-agglutination of *tularensis* may leave some doubt as to the proper interpretation of the serologic findings. *Tularemia* serum in most instances agglutinates *Bact. tularensis* in much higher dilution than those in which it agglutinates *Bact. abortus* or *Bact. melitensis*. In rare instances the employment of agglutinin absorption tests may be of value.

*Differential Diagnosis*—The signs and symptoms of *tularemia* are so similar to those of many other acute infectious diseases, notably influenza, typhoid, undulant fever and septicemia, as to make differential diagnosis difficult. Because of subcutaneous nodules, sporotrichosis has been suspected. Pathologists have called the malady tuberculosis because of the lesions in the lymph glands. When the disease is epidemic and typical cases are occurring, the possibility of *tularemia* should always be borne in mind. In the case of the primary cutaneous type of the disease the typical primary lesion with regional glandular involvement should easily differentiate it from other diseases. Any prolonged unexplained fever should suggest the possibility of *tularemia*. Primary atypical pneumonia in a locality where *tularemia* is prevalent should direct one's suspicion to the primary pulmonic type of the disease.

Hitherto any unilateral conjunctivitis with regional lymphadenitis was called Parinaud's conjunctivitis. A striking similarity and the absence of an established cause lead me to believe that many of the cases were actually instances of conjunctivitis *tularensis*. In 1924, Pascheff<sup>36</sup> suggested the substitution of the term "syndrome Parinaud" in place of "Parinaud's conjunctivitis" as signifying a unilateral conjunctivitis with regional adenitis.

Necrotic infectious conjunctivitis (Pascheff) is clinically similar to ophthalmic *tularemia* in many particulars. The acceptance of this disease as a clinical entity is not universal because of its close clinical

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<sup>36</sup> Pascheff, C. Differential Diagnosis Between Conjunctivitis Necroticans Infectiosa and Conjunctivitis *Tularensis*, *Am J Ophth* **10** 737, 1927.

similarity to ophthalmic tularemia, and because agglutination tests with *Bact tularensis* have not been carried out

The morphologic and cultural differences between the two organisms seem definitely to differentiate the two diseases. On the other hand, the striking similarity of the ocular and clinical symptoms and of the characteristic histopathologic changes lead me to believe that primary ophthalmic tularemia and necrotic infectious conjunctivitis are one and the same disease.

*Leptothrix conjunctivitis*, although clinically similar, differs as to etiology, *Leptothrix* being found in the pus and necrotic nodules.

*Sporotrichosis* is readily differentiated by its cultural characteristics.

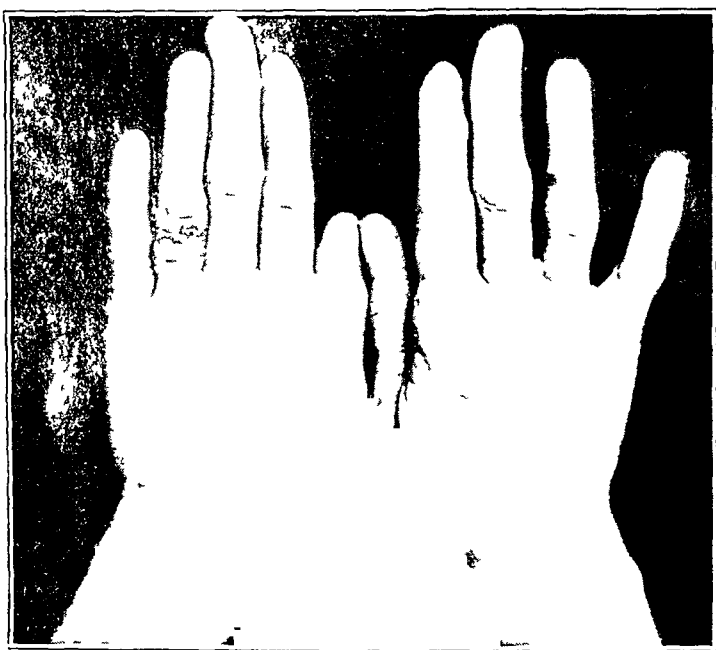


Fig. 11—An erythema multiforme-like eruption on the hands and face on the fourteenth day after the onset.

#### CONVALESCENCE

Weakness in proportion to the severity of the attending toxemia is an outstanding feature of the course and convalescence. Following a severe clinical course it is rare to see a patient at full time labor within three months. In my experience, a mild clinical course was noted in the majority of cases. Sixty-three per cent of the patients were either continuously ambulatory or able to be up and about within from thirty-six to forty-eight hours following the onset. Only 25 per cent were doing less than 50 per cent of their work at the end of three months. At the end of six months 10 per cent were unable to perform more than half time work and at the end of one year, 7 per cent were 25 per cent incapacitated because of fatigue and weakness.

## DEATHS

Five cases (4 per cent) terminated in death. One case of the primary ophthalmic type with early pulmonary involvement, marked toxemia and stupor terminated in death on the twelfth day of the disease. In a second case, of the cryptogenetic type, with primary pulmonary involvement, extreme toxemia, delirium and stupor, the patient died on the fourteenth day of illness. Coma accompanied by albuminuria

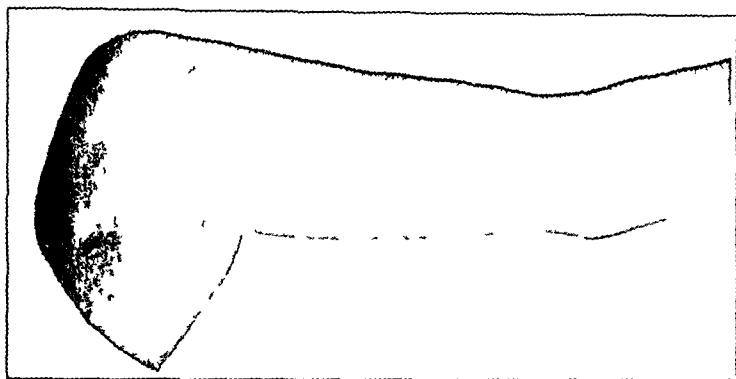


Fig. 12—Discrete elevated erythematous patches on the extensor surfaces of the arms three weeks after the onset

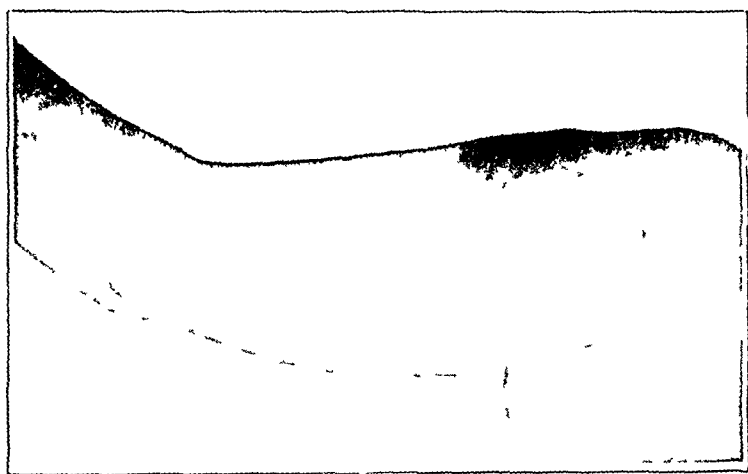


Fig. 13—A desquamating maculopapular eruption on the extensor surface of each arm on the twentieth day after the onset

and casts was the terminal condition in another case of the cryptogenetic type, death occurring during the ninth month. Death in the fourth case was preceded by a spontaneous pneumothorax, and occurred on the thirtieth day, following sudden acute pain in the chest. This was a case of the primary cutaneous type of the disease. In the fifth case, one of the primary cutaneous type of the disease, the patient manifested early pulmonary symptoms, delirium, stupor and cyanosis and died on the twenty-sixth day. The death rate in this series compares closely with previously reported figures.



## PROPHYLAXIS

Prophylaxis practically narrows down to the education of the public as to the dangers of the infection and the manner in which it is acquired. During an epidemic the early recognition of the disease in rodents is most important. Thorough cooking destroys the infective agent. The wearing of gloves by those who handle rabbits protects them to a certain extent. There have been 24 infections in laboratory workers in spite of all precautions.

*Preventive Inoculation*—Prophylactic vaccination against tularemia was successfully accomplished by Foshay.<sup>37</sup> Such vaccination is not practicable for general use but its apparent success recommends its use for those who come in close and frequent contact with infected animals.

## TREATMENT

The patient should be at rest in bed during the febrile stage of the disease. Large subcutaneous or intravenous injections of physiologic solution of sodium chloride seem best to allay the symptoms of delirium and severe toxemia. Healing of the primary cutaneous lesion does not seem to be enhanced by any local or systemic treatment. Incision increases the size of the primary ulcer and prolongs its healing. Exacerbation of the general systemic symptoms frequently follows this procedure. Suppurating nodules and glands should be adequately incised and drained only after suppuration is well advanced. Excision of the broken-down glands at this stage, followed by closure of the wound without drainage, is satisfactory. Antiseptics have little or no specific action on primary lesions in the conjunctiva. Hot applications and frequent lavage with warm physiologic solution of sodium chloride are perhaps the most satisfactory treatment.

Foshay<sup>38</sup> recently described the development of an apparently potent goat antiserum for the treatment of tularemia. The intravenous injection of about 10 cc of this "antitularense" serum on two successive days resulted in an abrupt cessation of fever, malaise, chills, sweats, arthralgia and myalgia, within forty-eight hours after the second injection. There also occurred a rapid reduction in the volume of the involved lymph nodes to an average of one-half their former diameters.

## SUMMARY

In addition to a short review of the literature, the characteristic clinical features in 123 cases of tularemia are presented, together with observations at autopsy in 1 case.

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<sup>37</sup> Foshay, L. Prophylactic Vaccination Against Tularemia, *Am J Clin Path* 27 (Jan) 1932.

<sup>38</sup> Foshay, L. Serum Treatment of Tularemia, *J A M A* 98 552 (Feb 13) 1932.

A new classification is presented. Sixty-nine cases occurred in males and 54 in females. One hundred and eight were of the primary cutaneous type, 6 were of the primary ophthalmic type and 9 were of the cryptogenetic type of the disease.

The average incubation period, definitely determined in 58 cases, was four and one-half days.

Sixteen cases presented pulmonary involvement. Primary and secondary pulmonary tularemia are discussed. The breast was involved in 2 cases. Thrombi in the veins were noted in 1 case. Pleurisy was a complication in 6 cases. Abdominal symptoms were prominent in 5 cases. Peritonitis was present in 1 instance. Delirium was a prominent feature in 6 cases. Acute mania complicated 1 case. In 1 case of the primary ophthalmic type optic atrophy occurred, with loss of vision in the affected eye. A purulent dacryocystitis complicated 1 case. Decided splenomegaly with perisplenitis was present in 5 instances. Osteomyelitis was observed once. Cervical adenitis as the only external evidence of the disease was observed in 4 cases. Subcutaneous nodules occurred in 28 instances. A cutaneous eruption was present in 23 cases (18.7 per cent).

There were 5 deaths indicating a mortality of 4 per cent in this series.

Other pertinent facts pertaining to the history, epidemiology, pathology, diagnosis and treatment are also discussed.

# THE SECOND POSITIVE WAVE OF THE QRS COMPLEX

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AND

SOLOMON R SLATER, M D

BROOKLYN

Great progress has taken place in the interpretation of electrocardiograms since their introduction. The evolution of the understanding of the significance of the Q R S complex, the R T and S T segments and the T wave has undergone many rapid strides, particularly during recent years, so that the recognition of pathologic variations from the usual normal appearance has become of considerable importance in detecting myocardial damage and abnormalities of the site of impulse production and of conduction and in the localization of cardiac infarction. Detailed attention to the description of the form and contour of the waves has yielded considerable information.

## VARIATION

The variation to be described involves the terminal portion of the S wave in lead III.

Of approximately 8 000 serial records taken from the cardiographic laboratory of the Jewish Hospital of Brooklyn, 320 revealed a positive finding. Of the latter, the data in 50 are herewith reported in a preliminary study with autopsy records in 3 cases. From a critical analysis of these records it has been repeatedly observed in lead III that following an R wave there is a downwardly directed (negative) S wave the upward limb of which rises to a variable distance above the iso-electric line in a sharp peak or summit and then descends with varying rapidity and a downward convexity to the iso-electric line, forming thereby a separate and distinct positive wave (fig 1). This wave may be sharp, pointed, slightly slurred or rounded at its apex, the catacrotic limb may be thickened or feathered. The height to which this wave mounts is variable, and at times may exceed the height of the preceding R wave in the same complex by as much as 5 mm. The contour of the descent of the wave is likewise variable, it may be a sharp and straight declivity merging at once with the so-called S T segment, or, as mentioned previously, it may descend gradually to the iso-electric line in a curving manner with a downward convexity. In its descent, the

trough of the wave may occasionally reach a level of from 0.5 to 1 mm above or below the iso-electric line, rarely, there may be a respiratory variation in its amplitude. Left axis deviation is found in each case. A Q wave in the ordinary sense, is not present. The nature of the S-T segment or the height and direction of the T wave which follows bear no relationship to the wave described.

#### CRITERIA

We have formulated tentatively the following criteria for the identification of this wave:

- 1 On standardization, there must be no overshooting (1 cm current equivalent to 1 millivolt)
- 2  $R_3$  must be a distinctly positive deflection above the iso-electric line

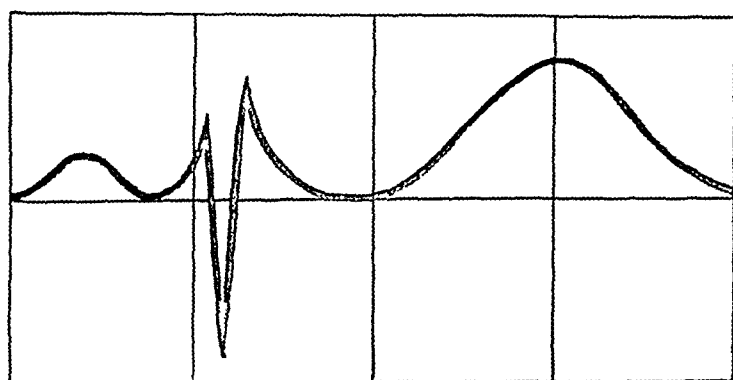


Fig. 1—Diagram of the second positive wave of the QRS complex of lead III, as described in the text

- 3  $R_3$  is followed by  $S_3$  of varying amplitude
- 4 The upward stroke of  $S_3$  rises above the iso-electric line in a positive peak or summit, as described, and then descends to the iso-electric level
- 5 Respiratory and frequency variations in the third lead are excepted

#### ANALYSIS OF CASES

The wave described appeared in 320 (4 per cent) of 8,000 records examined. A brief recapitulation of the data in the 50 cases studied is given in the table, with a description of the pertinent electrocardiographic features of the main complex. Briefly summarized it will be seen:

- 1 Twenty-eight (56 per cent) cases occurred in males, the average age being 49.1 years. The youngest male patient (case 34), a boy with acute glomerular nephritis of twelve weeks' duration, was 14 years of

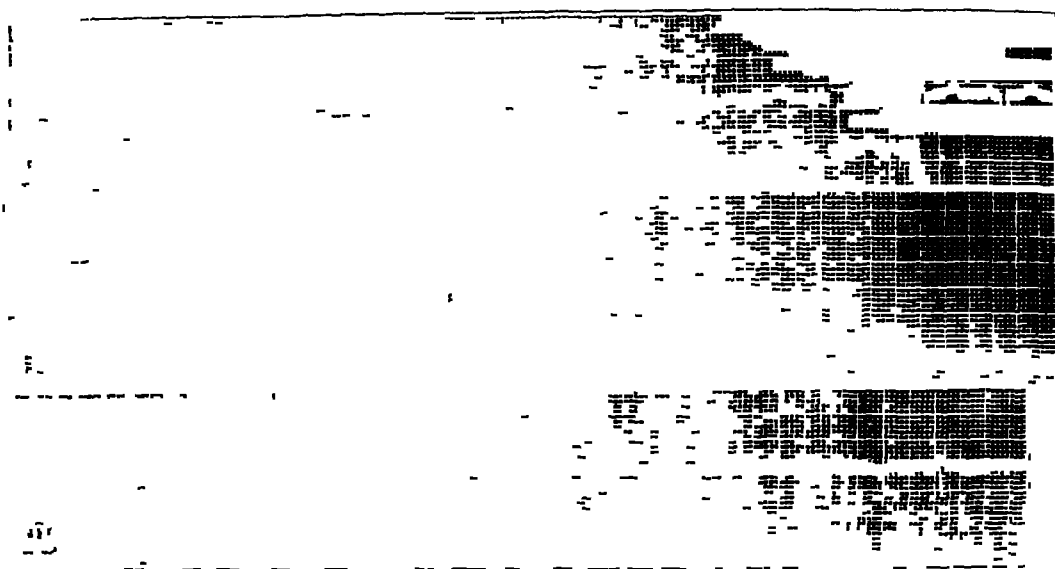


Fig 2 (case 4) —Electrocardiogram showing regular sinus rhythm, ventricular rate, 75,  $T_1$ , very sharply inverted, small main deflections, in lead II, slurred, PR interval in lead II, 0.16 second,  $T_3$ , high voltage and sharply pointed,  $S_3$ , main deflection, with changes in the height of the  $S_3$  with respiration. Impression: severe myocardial damage and left axis deviation. Diagnosis: diabetes mellitus and coronary thrombosis.

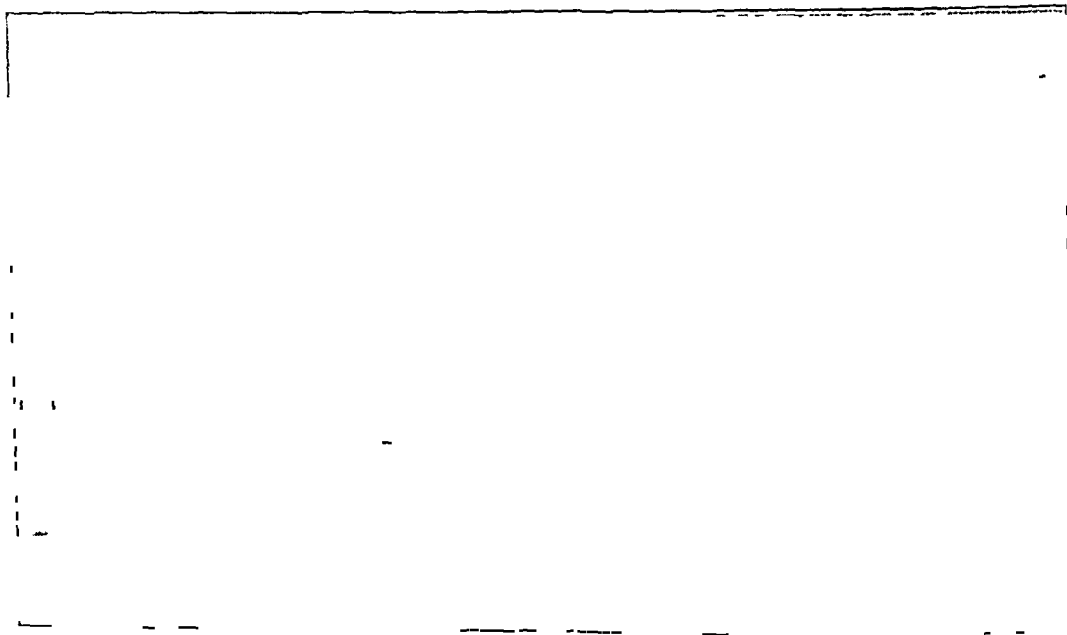


Fig 3 (case 7) —Electrocardiogram showing left axis deviation, regular sinus rhythm, average ventricular rate, 90,  $T_1$ , sharply inverted, PR interval in lead II, 0.16 second, T wave, low voltage, RT interval, depressed below the isoelectric line,  $S_3$ , main deflection. Impression: left axis deviation and myocardial damage. Diagnosis: carcinomatous transformation of a gastric ulcer with metastasis, myocardial fibrosis, aortic sclerosis, coronary thrombosis and sclerosis.

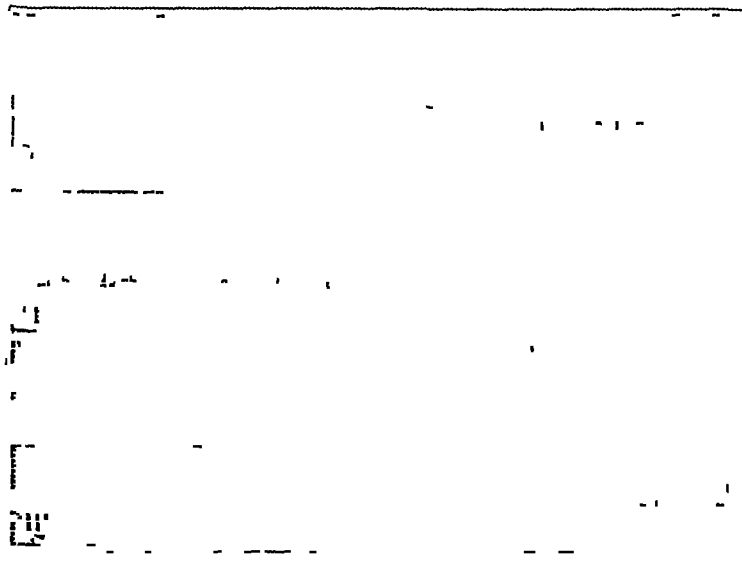


Fig 4 (case 8) —Electrocardiogram showing regular sinus rhythm, ventricular rate, 100, T wave in lead I, low voltage, poor R T transition in lead II, P R interval in lead II, 0.16 second, slurring of all main deflections,  $S_2$  main deflection in lead II. Impression myocardial disease and left axis deviation. Diagnosis rheumatic sepsis, endocarditis, myocarditis, pericarditis, effusion and pneumonia.



Fig 5 (case 9) —Electrocardiogram showing left ventricular predominance, T<sub>1</sub> inverted. Diagnosis acute rheumatic fever and tonsillitis.

age, the oldest (case 37), a man with generalized arteriosclerosis and chronic myocarditis, was 70 years of age

2 Twenty-two cases occurred in females (44 per cent), the average age being 45.6 years. The youngest patient in this group (case 6), a



Fig 6 (case 11) —Electrocardiogram showing regular sinus rhythm, ventricular rate 85,  $T_1$  inverted, P-R interval in lead II, 0.16 second, slurring of main deflection S. Impression: left axis deviation and definite myocardial damage. Diagnosis: coronary closure, fibrinous pericarditis and thrombophlebitis of the leg.

- Fig 7 (case 20) —Electrocardiogram showing ventricular rate, 79, lead I, normal, main complexes, slurred,  $S_1$  deep,  $T_3$  inverted, left ventricular predominance. Diagnosis: acute infectious polyarthritis and general arteriosclerosis.

girl with chronic rheumatic infection six years before admission, complicated by lobar pneumonia and migrating polyarthritis and pericarditis, was 17 years of age, two years before admission there had

been a recurrence in the form of pleurisy, and one year before admission, a recurrence in the form of rheumatic sepsis. The oldest patient in this group (case 31), a woman with generalized arteriosclerosis coronary and cerebral vascular sclerosis and hypertension, was 70 years of age.

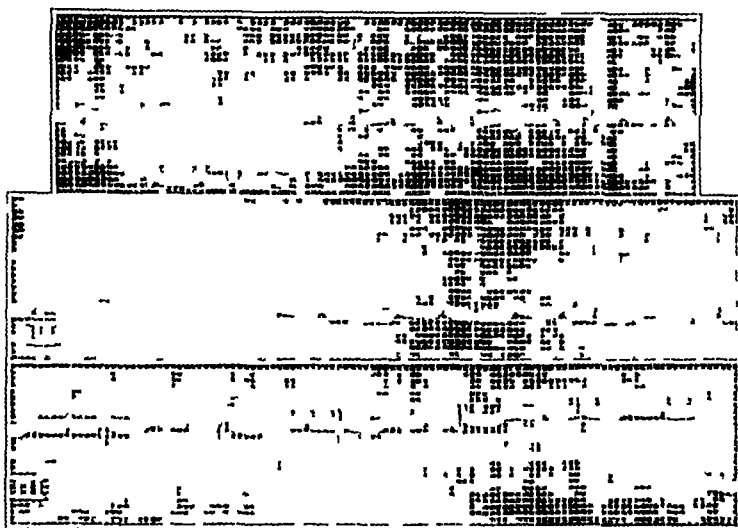


Fig 8 (case 23) —Electrocardiogram showing ventricular rate, 88 and regular sinus rhythm. Lead I P, up and widened, PR interval, 0.2 second, R, up and slightly slurred, RT, normal, and T, up. Lead II P, up, PR interval, 0.22 second, R, up, and ascending limb of R somewhat slurred, RT, normal, T, diphasic. Lead III P, up, PR interval 0.22 second, S, main deflection and slurred, T, inverted. Conclusion partial heart block. The slurring of the R waves and the diphasic T waves speak for some myocardial involvement even if the patient had been given digitalis. Diagnosis hypertension, recurrent rheumatic fever, chronic valvular disease and pericarditis.

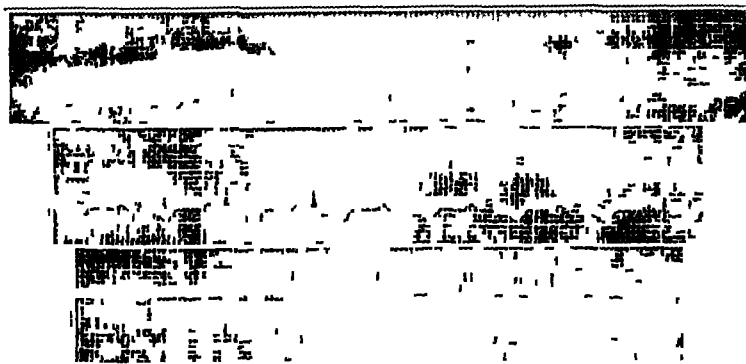


Fig 9 (case 45) —Electrocardiogram showing ventricular rate, 100. Lead I P, upright, PR interval, normal, R, slurred, ST, depressed, T, inverted. Lead II P, upright, high and widened, PR interval, normal, RS, diphasic and slurred, T, upright. Lead III P, upright, high and widened, PR interval, normal, S, deep and slurred, ST, and T, normal. Conclusion myocardial damage, auricular hypertrophy and left ventricular predominance. Diagnosis malignant disease of the lung and chronic rheumatic heart disease.



*Data on Fifty Cases, Including Electrocardiographic Features*

Case No.	Sex	Clinical Features	Duration Since age of	Clinical Diagnosis	Rate	P	QRS Amplitude	QRS Interval	Height of R <sub>s</sub>	R-T Interval	Direction of T Wave
1	F	Decompensation, pain, dyspnea, cough, recurrent rheumatic attacks	10 years	Chronic rheumatic valve disease with effusion	105	Up 1 mm	1 mm	0.08	2.5 mm	0.12	Up 5 mm
2	F	Pain, swelling, disability of the hand	4 days	Acute rheumatic fever	110	Up 3 mm	6 mm	0.06	2 mm	0.10	Down 2 mm
		General aches and pains, migratory to joints, sweats preceding pains, dyspnea	3 weeks	Polyarthritis							
3	M	Hematuria	2 weeks	Malignant hypertension	107	Up 1 mm	3.5 mm	0.06	1 mm	0.12	Up 1 mm
		Hemiplegia	1 day	General arteriosclerosis							
		Headache	Many years	Nephrosclerosis, hematuria							
4	M	Diabetes	1 year	Diabetes mellitus, coronary thrombosis	75	Diphasic	7 mm	0.07	3 mm	0.08	Up 7 mm sharp
		Dyspnea and precordial pain	8 months								
		Sudden attack	5 days ago								
5	F	Recurrent rheumatic fever	Since age of 25 years	Recurrent arthritis of chronic articular rheumatic fever, chronic rheumatic valvular endocarditis	75	Down 1 mm	6 mm	0.06	1.5 mm	0.21	Down 1 mm
		Cold, sore throat, arthritis, fugacious pains	4 weeks	osteo arthritis							
6	F	Grip	6 years ago	Chronic rheumatic infection, lobar pneumonia	100	Up 1 mm	8 mm	0.04	2.5 mm	0.14	Down 1 mm
		Recurrent attacks of painful joints, fever and sore throat, nephritis, pneumonia and pleurisy	2 years ago	migrating polyarthritis, old pericarditis							
7	M	Dyspnea, substernal pain and oppression, weakness	1 year ago	Carcinomatous transformation of gastric ulcer with metastasis, myofibrosis, aortic sclerosis, coronary thrombosis and sclerosis	90	Up 1 mm	8 mm	0.08	1.5 mm	0.12	Up 3.5 mm
		Right sided pain and loss of 12 pounds (5.4 kg)	3 months								
8	F	Pains in joints and fever, sore throat and rash	5 days	Rheumatic sepsis endocarditis, myocarditis, pericarditis, effusion, pneumonia	100	Up 2 mm	8 mm	0.06	3.5 mm	0.14	Up 5 mm
9	M	Multiple pains and swelling in joints	2 1/2 years ago	Acute rheumatic fever, chronic tonsillitis	75	Iso electric	5 mm	0.06	2.5 mm	0.18	Down 1 mm
		Recurrence of same symptoms plus chill, headache and sore throat	1 week								

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*Data on 115 Cases Including Electrocardiographic Features -Continued*

Case No.	Sex	Clinical Features	Duration	Chief Diagnosis	Rate	P	P-R	Q-R-S Amplitude	Height of R wave	R-T Inter val	Direction of Wave
22	F	Epigastric pain after meals Dyspnea on exertion, precordial oppression and palpitation	6 weeks 6 weeks	General arteriosclerosis, coronary sclerosis, myocardial fibrosis, dyslipidatutism, chronic cholecystitis	80	Up 1 mm	0.16	3.5 mm	0.05	0.14	Up 1 mm
23	F	Idioma Dyspnea on exertion Dyspnea and paroxysmal nocturnal dyspnea and palpitation	7 years 9 years 1 year	Hypertension, recurrent rheumatic fever, chronic valvular disease, pericarditis	88	Up 2 mm	0.22	3.5 mm	0.04	1 mm	Down 1 mm
24	F	Precordial oppression and heaviness Epigastric pain Cardiac disease Recurrent attacks of orthopnea and dyspnea Same symptoms Diabetes	Past year 1 month 6 years 3 months 3 weeks 4 years 4 days	Diabetes mellitus, acidosis postoperative adhesions, neurasthenia, chronic cholecystitis	100	Up 0.5 mm	0.20	5 mm	0.04	1.5 mm	Down 0.5 mm
25	M	Oppression in chest, especially several times, with weakness	4 years	General arteriosclerosis, coronary sclerosis, chronic bronchitis and emphysema	70	Up 1.5 mm	0.18	2 mm	0.08	1.5 mm	Up 1 mm
26	M	Orthopnea and precordial choking Symptoms recurred Precordial pain and precordial pain in right upper quadrant Precordial pain and choking Frontal headache and vertigo	5 years 6 days 3 years 3 months 3 years	Paroxysmal ventricular tachycardia, coronary sclerosis, chronic myocarditis	75	Up 1.5 mm	0.20	6 mm	0.06	1.5 mm	Up 1.5 mm
27	F	Pain in right upper quadrant Precordial pain and choking Frontal headache and vertigo	3 months 3 years	Generalized arterio sclerosis, cardiac arteriosclerosis, coronary sclerosis	88	Diphasic 1 mm	0.16	3 mm	0.04	2 mm	Down 1 mm
28	M	Nausea, headache, vertigo, weak legs Similar attack Gastrointestinal symptoms	18 years 4 months 4 months	Generalized arterio sclerosis, neurasthenia, chronic constipation	100	Up 0.5 mm	0.16	5 mm	0.12	2.5 mm	Up 1.5 mm
29	F	Epigastric pain Vomiting Hemoptysis Headache, vertigo, blurred vision Weakness increased Pain in left lower quadrant	2 weeks 4 hours 22 years ago 1 year 1 year 2 weeks	Pyelocystitis, ureteral calculus, chronic myocarditis	125	Up 1 mm	0.14	7 mm	0.06	1 mm	Up 2.5 mm sharp

[illegible]

*Data on Fifty Cases Including Electrocardiographic Features—Continued*

Case	Age	Sex	Clinical Features	Duration	Clinical Diagnosis	Rate	P	P R	QRS Amplitude	QRS Interval	Height Of R <sub>2</sub>	R <sub>2</sub> T <sub>1</sub> Interval	Direction of T Wave
13	45	M	Abdominal pain Pain in right shoulder Pain in left shoulder, radiating down to arm and fingers many times	1 week 3 months 6 weeks	Acute suppurative cholecystitis, acute hepatitis and angina pectoris	100	Up 2 mm	0 16	6 mm	0 06	3 mm	0 20	Biphasic
14	46	F	Pain in joints and sore throat Rheumatic polyarthritis Recurrence of same symptoms	3 weeks At 15 years At 24 years	Acute and rheumatic polyarthritis, rheumatic heart disease, mitral regurgitation	84	Down 2 mm	0 16	3 mm	0 04	3 mm	0 16	Down 2 5 mm
15	52	M	Hemoptysis Weakness Rheumatic fever Marked dyspnea	9 months 2 months 1014 9 months	Valvular disease of the lung, chronic rheumatic heart disease	100	Down 1 mm	0 12	12 mm	0 10	4 mm	0 16	Down 1 mm
16	60	F			Chronic glomerular nephritis, general arteriosclerosis, hypertension cardiac hypertrophy and dilatation, coronary sclerosis, myocardial fibrosis, general anasarca	88	Down 0 25 mm	0 12	4 mm	0 04	1 5 mm	0 18	Up 0 5 mm
47	19	M	Fugacious arthritis Slight exertional dyspnea Epistaxis at long intervals	5 years 5 years 2 years	Gouty's splenomegaly osteoarthritis	100	Diphasic 0 5 mm	0 12	8 mm	0 04	3 mm	0 12	Down 3 mm sharp
48	57	F	Heaviness and abdominal distention with belching after meals Headache Edema of ankle Precordial pain and sticking on exertion	2 years 1 year 1 year	Arteriosclerosis, hypertension, myocardial degeneration and insufficiency	65	Up 1 mm	0 16	9 mm	0 12	3 5 mm	0 16	Down 2 mm
49	36	M	Sore throat, pain in muscles and joints Exertional dyspnea, sticking exertional precordial pain, epistaxis, night sweats	6 days Many years	Recurrent rheumatic fever subacute arthritis, coronary sclerosis, angina pectoris, coronary arteritis	100	Up 1 mm	0 16	3 5 mm	0 06	3 5 mm	0 10	Up 3 mm
50	45	F	Jaundice Precordial pain Numbness Precordial pain, palpitation and edema	16 years ago 1 week ago 1 day ago 1 year	Chronic cholecystitis chronic myocardial insufficiency	84	Up 1 mm	0 12	5 mm	0 06	1 5 mm	0 20	Down 1 mm

3 In 86 per cent, there was clinical evidence of cardiac disease. Of the remaining 7 patients (14 per cent), 5, without symptoms, were between the ages of 40 and 54 years, an age group in which cardiovascular diseases are usually present. The 2 remaining patients were

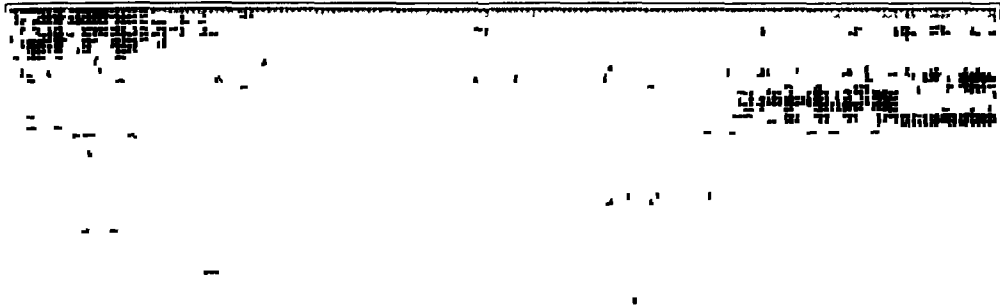


Fig 10 (case 47) —Electrocardiogram showing ventricular rate, 100. Lead I P, upright, PR interval, normal, R, ST and T, normal. Lead II P, normal, PR interval, normal, R, ST and T, normal. Lead III P, biphasic, S, deep, T, sharply inverted. Conclusion: left ventricular predominance, sharp inversion of T. Diagnosis: Gaucher's splenomegaly and osteo-arthritis.

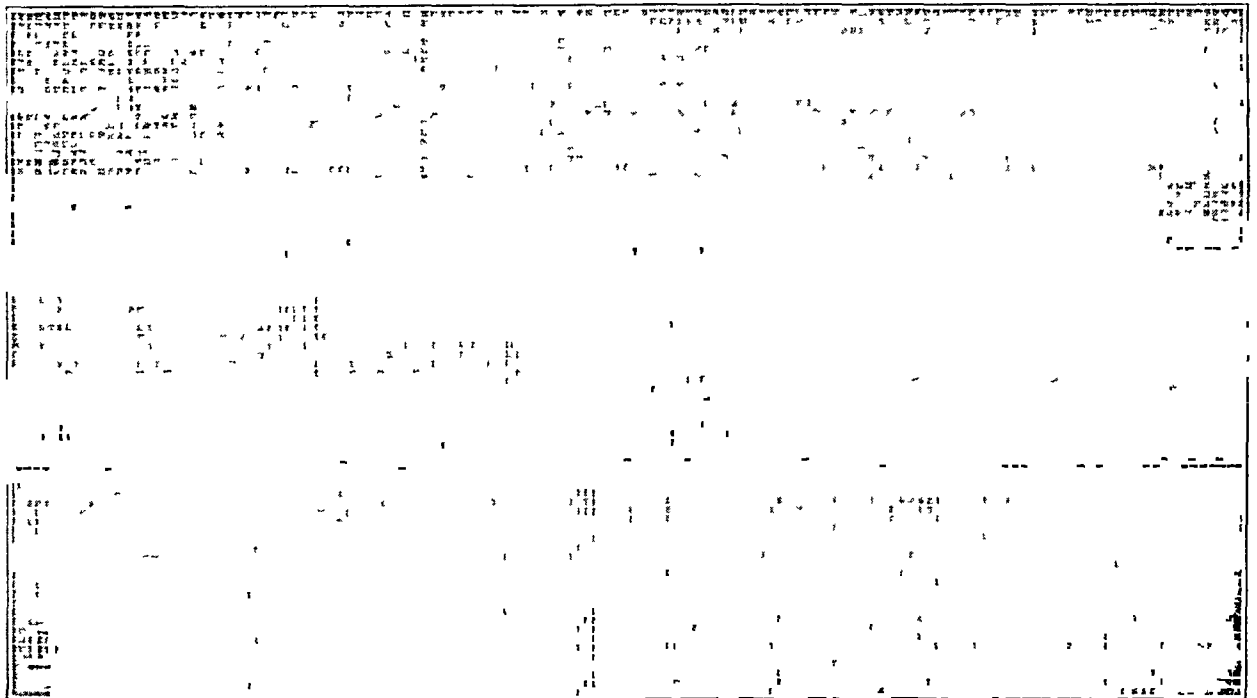


Fig 11 (case 48) —Electrocardiogram showing ventricular rate, 65, and regular sinus rhythm. Lead I P, up, PR interval, 0.16 second, R, up and somewhat slurred, widening of the QRS, ST, normal, T, up. Lead II P, up, PR interval, 0.16 second, R, low and slurred, T, up and very low, almost iso-electric. Lead III P, biphasic, PR interval, 0.12 second, S, main deflection and slurred, ST, transition, poor, T, inverted. Conclusion: left ventricular predominance and myocardial involvement. Diagnosis: arteriosclerosis, hypertension and myocardial degeneration and insufficiency.

14 and 19 years of age, respectively. The former suffered from acute glomerular nephritis, the latter from Gaucher's splenomegaly, in which there were cardiac symptoms.

We have diligently searched the literature but have failed to find a previous description of this electrocardiographic alteration. Einthoven, in his original contributions on the electrocardiogram and in his later studies makes no mention of it,<sup>1</sup> nor did Kraus and Nicolai,<sup>2</sup> Eyster and Meek in an exhaustive and critical analysis,<sup>3</sup> Carter,<sup>4</sup> Lewis,<sup>5</sup> Master and Pardee,<sup>6</sup> Fahr,<sup>7</sup> Oppenheimer and Rothschild,<sup>8</sup> Levine,<sup>9</sup> Dieuaide<sup>10</sup> and Williams<sup>11</sup> have not referred to this variation in the many papers which they have published, and yet illustrations and numerous electrocardiograms identical with those here described are exhibited.

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## SUMMARY

1 In a critical analysis of 8,000 electrocardiograms there is described in 320 (4 per cent) a second positive wave following  $S_3$ . Left axis deviation was constantly present.

2 Analysis shows that at least 86 per cent indicated change in the cardiac muscle, and in 14 per cent such changes may have been present.

3 Neither sex nor age seems to account for the presence of the wave, though there was a slight predominance in males.

4 In an extensive review of the literature, no previous description of this electrocardiographic abnormality has been found.

## CONCLUSIONS

1 The second positive wave of the QRS complex is found with great regularity in electrocardiograms made in cases of myocardial disease.

2 It has not been found in a study of the abnormal electrocardiogram.



# ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF ACUTE LOBAR PNEUMONIA

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Since 1921 when Friedmann<sup>1</sup> reported that artificial pneumothorax was a valuable procedure in the treatment of lobar pneumonia, isolated reports of various observers have been published that substantiate his claims. Recently Lieberman and Leopold<sup>2</sup> reviewed the results of fifty published cases and found a mortality of only 6 per cent. More striking than the low mortality figure is the dramatic symptomatic relief which is consistently produced by this measure. Coghlan<sup>3</sup> reported that with pneumothorax he was able to produce a crisis which simulated a natural crisis. The improvement was maintained by the employment of subsequent refills. Support for these optimistic clinical results is presented by Lieberman and Leopold, who carried out experiments with dogs. Producing lobar pneumonia by the Robertson method, they noted a mortality of 16 per cent in the group treated by pneumothorax and a mortality of 72 per cent in the control group.

The lack of a rational explanation of the beneficial results has caused concern to most of the observers. Coghlan ventured the following explanation: (1) Relief from pain and dyspnea is produced by a separation of the inflamed pleural surfaces, (2) the inflamed lung is placed at rest, (3) toxins are prevented from entering the general circulation, and anoxemia is diminished because the procedure limits the flow of blood through the lung.

Possible dangers were discussed by Coghlan and Lieberman. They agreed that circulatory collapse may be initiated as the result of cardiac and mediastinal displacement. There have been no reports of pleural shock, pyopneumothorax, pulmonary abscess, pulmonary gangrene, pulmonary embolism or septicemia as complications of the treatment.

We have used artificial pneumothorax as a therapeutic measure on twelve patients with lobar pneumonia at Cook County Hospital. The patients were selected from a group of eighteen admitted to the ward during the period of the study. Six patients were excluded for the

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From the Cook County Hospital and Northwestern University Medical School

1 Friedmann, U. *Deutsche med Wchnschr* **47** 443, 1921

2 Lieberman, L. M., and Leopold, S. S. *Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs*, *Am J M Sc* **187** 315, 1934

3 Coghlan, J. J. *Treatment of Acute Lobar Pneumonia by Artificial Pneumothorax*, *Lancet* **1** 13 (Jan 2) 1932

following reasons Two showed bilateral involvement, two had bronchopneumonia, in one there was a suggestion of apical tuberculosis, and one was in a dying state when admitted The technic was like that described by Coghlan<sup>3</sup> To exclude bilateral pulmonary involvement and

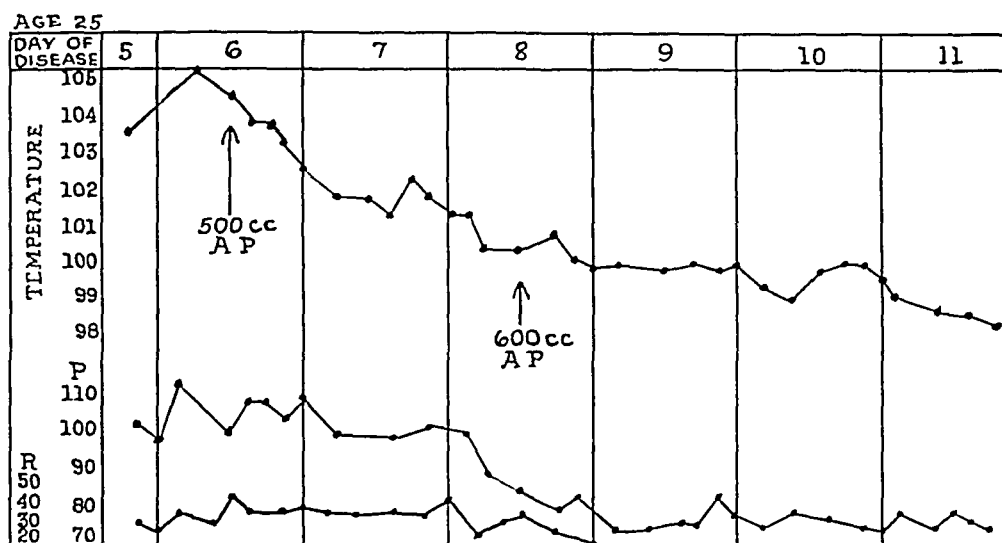


Fig 1 (case 1)—Pneumonia of all of the lobes of the right lung There was immediate relief from pain and dyspnea Sweating was profuse Recovery was uneventful AP signifies artificial pneumothorax, R, respiratory rate, P, pulse rate

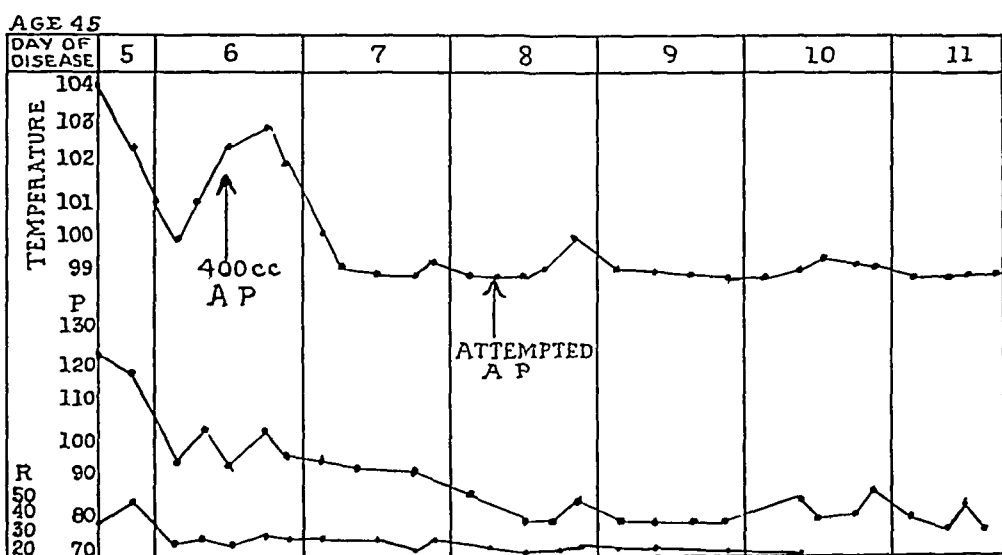


Fig 2 (case 2)—Pneumonia of the right upper lobe The leukocyte count was 23,000 on the sixth, and 20,000 on the seventh day of the disease Spectacular relief from pain, dyspnea and the toxic appearance took place There was a positive pleural pressure on the second attempt to refill Recovery was uneventful

confirm the diagnosis, preliminary roentgen films were made Within eight hours after pneumothorax and just prior to discharge roentgen films were again made

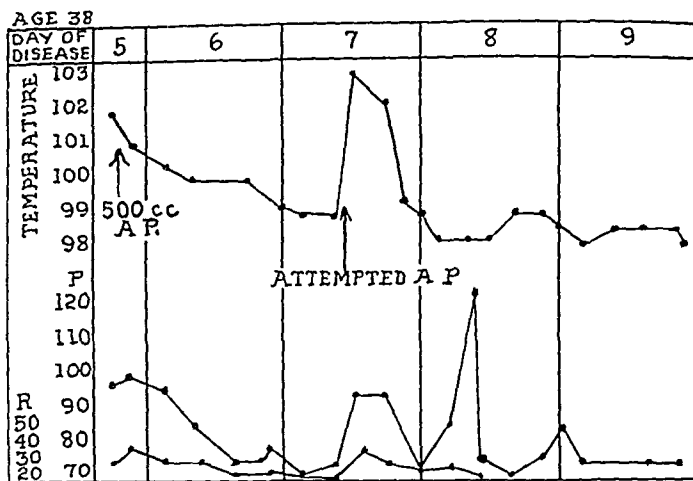


Fig 3 (case 3)—Pneumonia of the left lower lobe The leukocyte count was 12,200 on the fifth day and 17,200 on the eighth The crisis was typical, with complete symptomatic relief There were no complaints during the rise in fever on the seventh day Recovery was uneventful

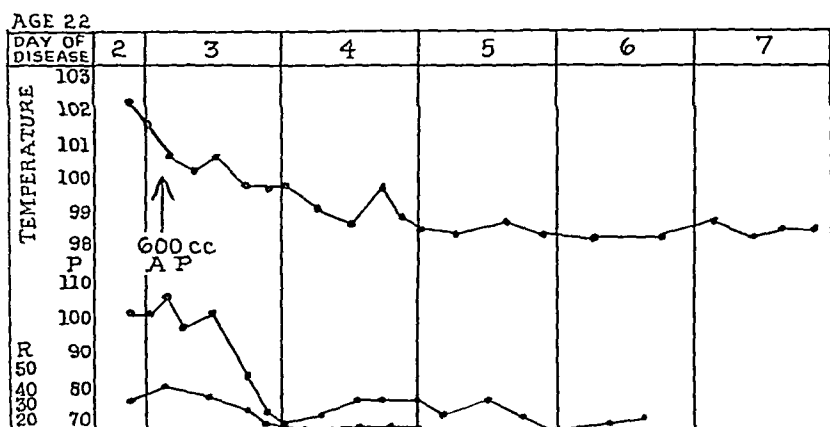


Fig 4 (case 4)—Pneumonia of the right lower lobe The leukocyte count was 20,100 on the third day and 17,450 on the fifth The crisis was spectacular, and the symptomatic relief immediate

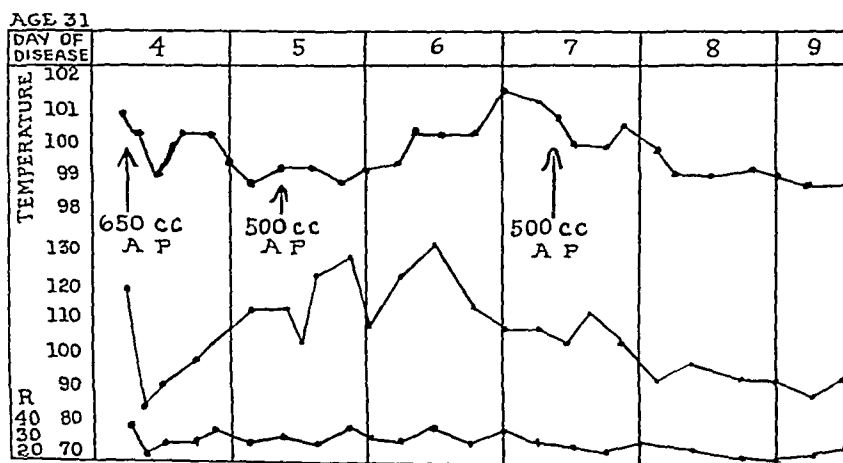


Fig 5 (case 5)—Pneumonia of the left upper lobe There were delirium tremens and meningismus The patient's condition was highly toxic and he perspired profusely after each pneumothorax Relief from delirium was gradual

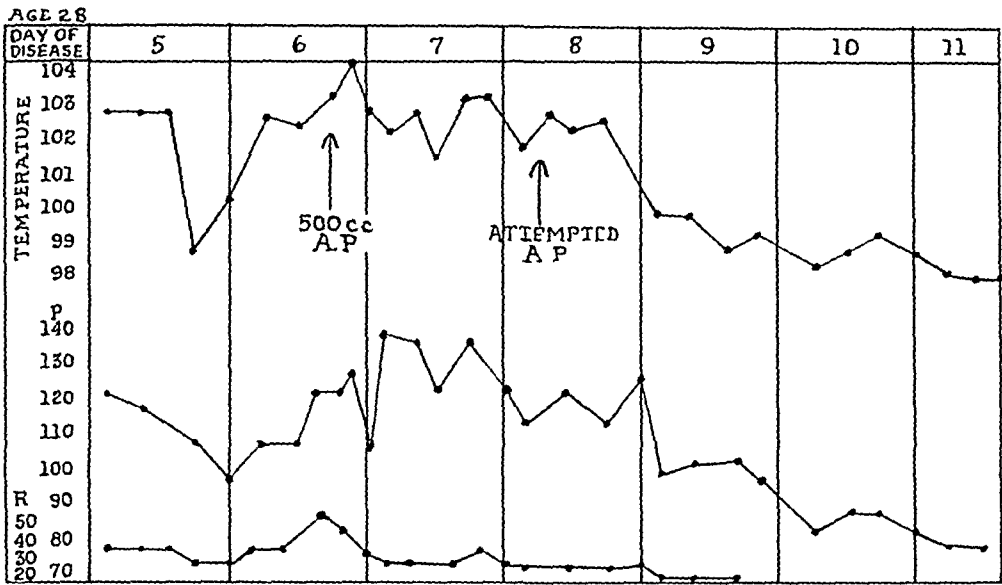


Fig 6 (case 6) —Pneumonia of all of the lobes of the right lung The leukocyte count was 27,200 on the sixth day, 24,400 on the eighth day and 25,300 on the ninth day The patient was profoundly toxic, there were marked pain, severe hiccups and jaundice Friedlander's bacilli were present in the sputum The pain and the hiccups were stopped by the pneumothorax The jaundice persisted until the eleventh day Recovery was uneventful

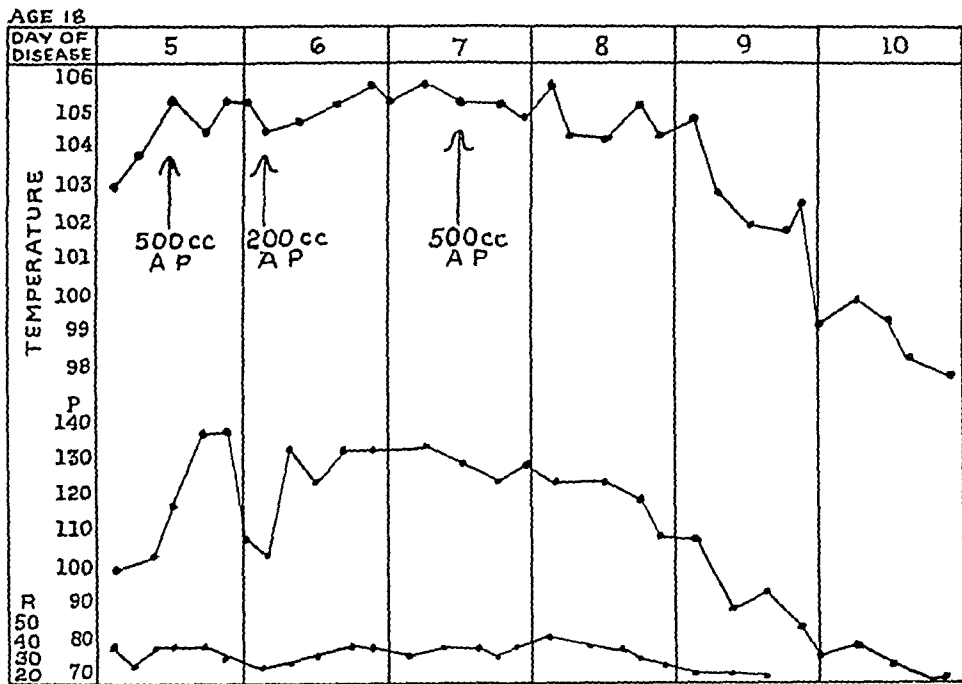


Fig 7 (case 7) —Pneumonia of the left lower lobe The leukocyte count was 23,200 on the fifth, 24,000 on the sixth, 26,000 on the seventh and 25,000 on the eighth day Perspiration was profuse Relief from pain occurred after the first pneumothorax Recovery was good

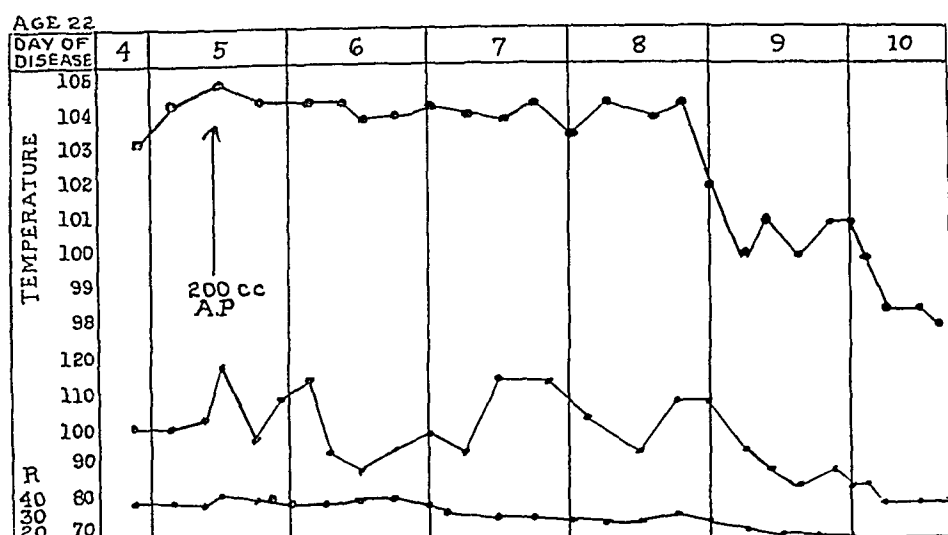


Fig 8 (case 8) —Lobar pneumonia of all of the lobes of the right lung The leukocyte count was 15,000 on the fourth day and 13,800 on the seventh The pneumothorax was limited to 200 cc of air because the pressure was positive Slight sweating and relief from pain occurred Recovery was uneventful

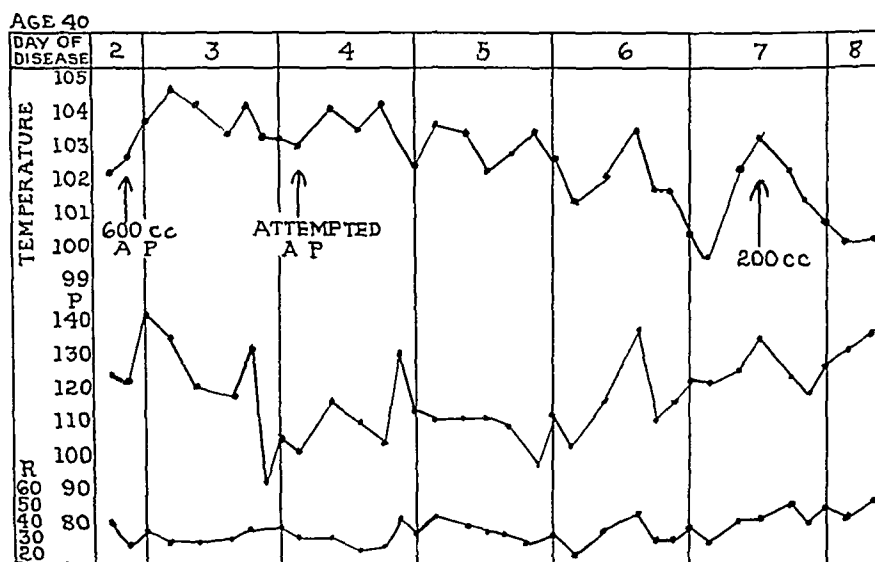


Fig 9 (case 9) —Pneumonia of the right lower and upper lobes The first pneumothorax caused perspiration and relief from pain At the second pneumothorax pleural fluid was encountered Consolidation of the left upper lobe occurred two days before death, and there was terminal meningismus Autopsy was performed

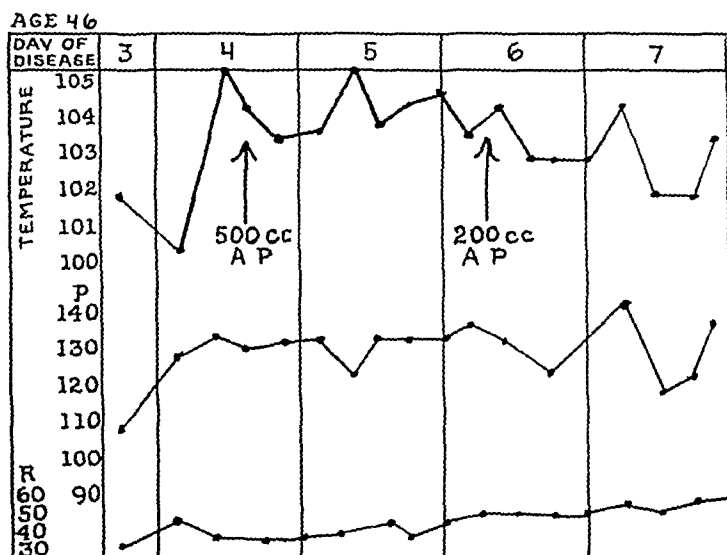


Fig 10 (case 10)—Pneumonia of the left lower lobe The leukocyte count was 15,000 on the third day and 22,000 on the sixth The patient had delirium tremens, he was toxic and dyspneic and presented marked cyanosis There was no improvement after pneumothorax Death occurred Autopsy was not performed

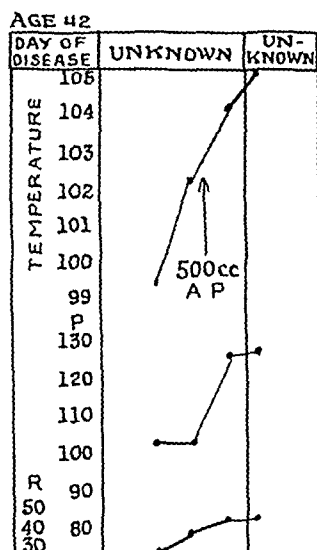


Fig 11 (case 11)—Pneumonia of the right upper lobe The patient had delirium tremens, there was deep cyanosis but no sweating Death occurred No autopsy was performed

#### RESULTS

The results obtained were not so good as those obtained by other investigators As shown by the charts, four patients (figs 1 to 4) obtained immediate symptomatic relief that was quickly followed by a lowering of the fever and of the pulse rate, four patients (figs 5 to 8) obtained symptomatic relief, but there was little or no lowering of the fever or pulse rate, and four patients (figs 9 to 12) died

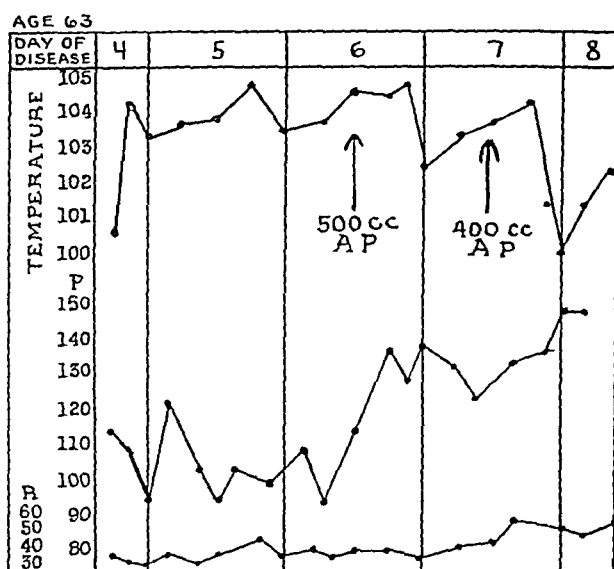


Fig 12 (case 12)—Pneumonia of all of the lobes of the right lung. The leukocyte count was 12,450 on the fourth day, 6,600 on the sixth day and 6,100 on the seventh day. The patient was an emaciated old man, with marked generalized arteriosclerosis, there was no symptomatic relief. Death occurred. Autopsy was not performed.

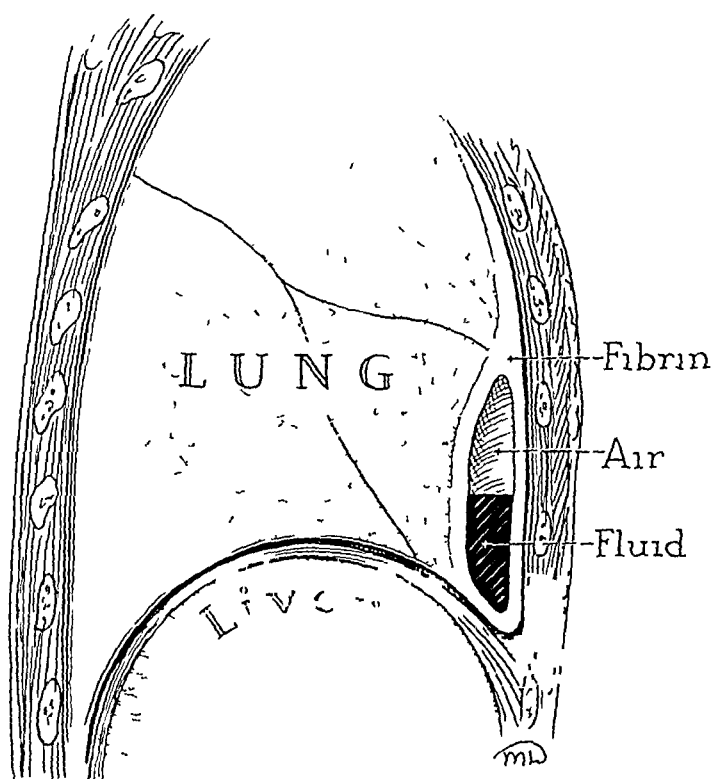


Fig 13 (case 9)—Drawing illustrating the localized pneumothorax.

## REPORT OF FATAL CASES

CASE 9—A white man, aged 40, with involvement of the upper and lower lobe of the right lung, received 500 cc of air by artificial pneumothorax on the second day of the disease. A refill on the third day was unsuccessful, and physical examination revealed evidence of pneumothorax on succeeding days, until the seventh day, when 200 cc of air was again introduced into the pleural cavity. The patient died on the eighth day. Autopsy revealed lobar pneumonia in a stage of gray hepatization in all of the lobes of the right lung and a patch of early pneumonia in the upper lobe of the left lung. An extensive, thick layer of fibrin covered all parts of the right lung, especially anteriorly, and extended over the anterior mediastinum. Anterior and lateral to the right lower lobe in this dense mass of fibrin was a completely walled-off pocket which contained 150 cc of purulent fluid and a similar quantity of air.

CASE 10—A colored man, aged 46, chronically alcoholic, was admitted in a state of delirium tremens, he was profoundly dyspneic and cyanotic. Roentgeno-

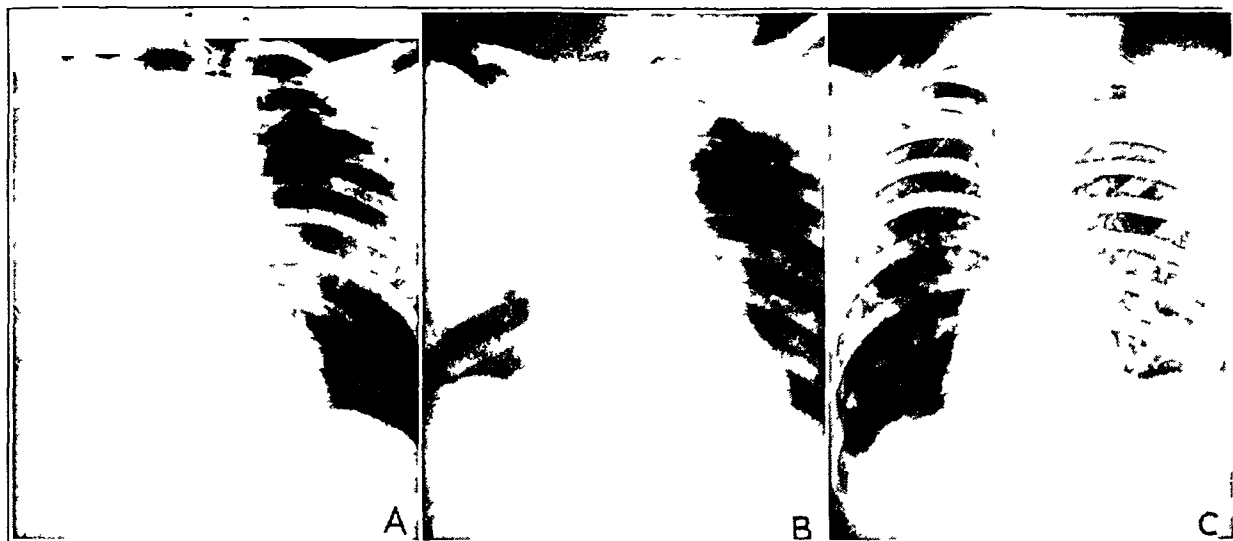


Fig 14 (case 1)—*A*, Roentgenogram taken before the pneumothorax, *B* roentgenogram taken four hours after the pneumothorax, and *C*, roentgenogram taken eight days after the crisis, showing no harmful residue.

grams revealed involvement of the left lower lobe. No relief was obtained from artificial pneumothorax on the fourth and sixth days of the disease. The patient died on the seventh day. No autopsy was made.

CASE 11—A white man, aged 42, was admitted in a state of delirium tremens. He received pneumothorax four hours after admission and died four hours later. The dyspnea, cyanosis and toxic appearance were neither improved nor adversely affected by the pneumothorax.

CASE 12—An emaciated man, aged 63, with generalized arteriosclerosis received pneumothorax on the sixth and seventh days of the disease. The preliminary roentgenograms revealed involvement of practically all of the right lung. No symptomatic relief was obtained, and the patient died on the eighth day. Autopsy revealed not only lobar pneumonia involving all of the lobes of the right lung but a large patch of bronchopneumonia in the lower lobe of the left lung. There was no air in the right pleural cavity and only slight fibrinous pleuritis.



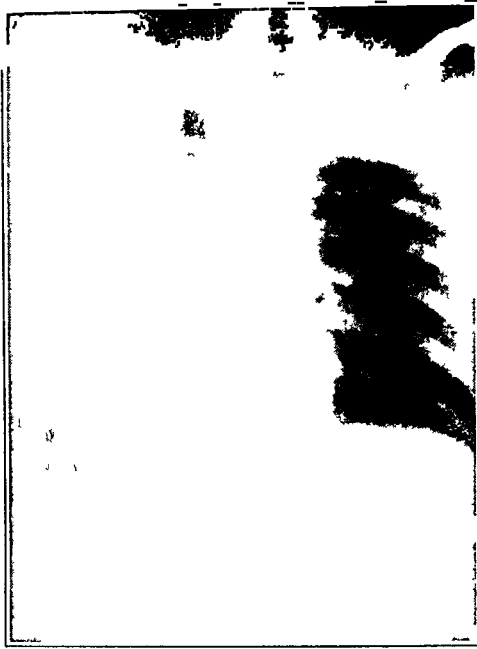


Fig 15 (case 5) —Roentgenogram taken four hours after the pneumothorax. Note the air around the apex and the base.

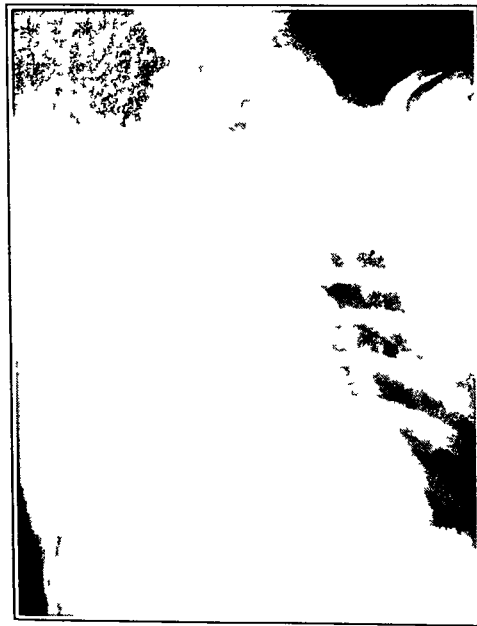


Fig 16 (case 6) —Roentgenogram taken six hours after the pneumothorax. Note the elevation of the lung above the diaphragm. Relief from hiccup was obtained.



Fig 17 (case 7) —Roentgenogram showing considerable pulmonary collapse



Fig 18 (case 9 —Roentgenogram taken after the first pneumothorax The patient died

## ROENTGEN STUDIES

As a precautionary measure to eliminate bilateral involvement no treatment was given until after roentgenograms were made. Films were repeated within from four to twelve hours after the pneumothorax and again prior to discharge from the hospital. The localization of the air and its effect on the lung varied widely. Figure 14 shows reproductions of roentgenograms made of the patient in case 1. A large pocket of air was present around the lower lobe, and a smaller amount outlined the medial border and apex. It is possible that the diffuse distribution of the air and the partial collapsing effect on the lower lobe account for the favorable results in this case. Figure 15 shows air around the apex and the base in case 5, but there was no crisis produced in this case. Figure 16 reveals air around the lower lobe, with separation of the diaphragm and the lung (case 6). Immediate relief from hiccups was a feature in this case. Figure 17 (case 7) reveals more extensive pulmonary collapse than was present in the other cases, and yet the procedure effected no relief from the fever. Figure 18 (case 9) reveals a large quantity of air present following the initial pneumothorax in a patient who subsequently died with the pleural cavity completely obliterated by fibrin.

## COMMENT

When one is studying an individual case or a small series of cases of lobar pneumonia, it is difficult to evaluate the effect of any type of treatment. It is particularly difficult to evaluate a crisis-inducing therapeutic measure when it is applied on the fifth day of the disease or later. Such was the case in most of the patients of this series. Even the spectacular results obtained in case 4 on the second day of the disease might properly be thought of as a natural crisis, since crises occasionally develop at this early stage. The effect of artificial pneumothorax on the mortality rate cannot be determined from this series or from previously published reports of cases, because the cases were selected and the severer forms (bilateral) eliminated. In this connection the higher mortality rate experienced in our study properly might be attributed to bad judgment in the selection of patients. Thus our group of patients with fatal cases included an emaciated old man with arteriosclerosis, two alcoholic patients with delirium tremens and a man in whom pneumonia developed later in the opposite lung.

Careful analysis of the fatal cases in this series reveals no proof that pneumothorax aggravated the disease or contributed to the fatal outcome. However the postmortem observations in one patient (case 9) suggest that marked fibrinous pleunitis and pyopneumothorax may be stimulated by the procedure. The development after artificial pneumothorax of lobar pneumonia of the opposite lung in one patient and bron-

chopneumonia in the opposite lung of another patient also suggests a possible hazard

In spite of these insinuations of doubt, one cannot escape the fact that immediate relief from pain and dyspnea is a striking effect of artificial pneumothorax in lobar pneumonia. Immediate relief from hiccups was also observed once. Profuse sweating like that seen in a natural crisis was usually produced within a few minutes after the pneumothorax. No consistent effect on the leukocyte count was demonstrated. The widespread distribution of air in the pleural cavity after pneumothorax and the relatively small amount of pulmonary collapse

*Lower Limits of Water Pressure Before and After Pneumothorax in Twelve Selected Patients*

Case	Date	Lower Limits of Water Pressure Before Pneumothorax	Quantity of Air, Cc	Lower Limits of Water Pressure After Pneumothorax
1 J H	3/ 6	— 5	400	+ 2
2 J N.	2/21	— 6	500	— 2
	2/26	— 4	600	— 1
3 R K	2/16	— 8	600	0
	2/21	— 3	200	+ 4
4 H G	1/25	— 2	400	+ 8
	1/27	+ 2	0	
5 A D	2/13	— 6	500	— 2
	2/15	+ 1	0	
6 G W	2/12	— 3	500	0
	2/14	+ 2	0	
7 M B	2/15	— 5	500	0
	2/17	— 4	500	0
8 R G	2/14	— 5	600	0
9 J O	2/ 7	— 7	650	0
	3/ 8	— 4	500	+ 2
	3/10	— 4	500	— 2
10 R N	3/ 6	— 6	500	— 1
	3/ 8	— 3	200	+ 6
11 F P	3/12	— 2	200	+ 8
12 O H	3/ 5	— 4	500	0
	3/ 6	— 4	400	+ 2

seem to indicate that the symptomatic relief depends on the separation of visceral and parietal pleura and partial immobilization of the lung. No explanation of the sweating phenomenon is indicated.

#### SUMMARY

Twelve selected patients with acute unilateral lobar pneumonia were treated by artificial pneumothorax. Nine received immediate symptomatic relief from pain and dyspnea. It appeared that the procedure brought on an artificial crisis in four patients. Four (33 per cent) died, and necropsies revealed an early pneumonia in the opposite lung of two patients. A localized pyopneumothorax was present at necropsy near the site of thoracentesis in one patient.

# CIRCULATION TIME IN FAILURE OF THE LEFT SIDE OF THE HEART

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AND

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Increased attention has been devoted of late to the old clinical concept of left ventricular failure. Excellent surveys have been reported by White<sup>1</sup> and by Weiss and Robb<sup>2</sup>. The clinical manifestations are those resulting from pulmonary engorgement, and include various combinations of the following: exertional dyspnea, cardiac asthma, orthopnea, cyanosis, cough, blood-streaked sputum, physical signs and roentgen evidence of pulmonary engorgement, diminution in vital capacity, pulmonary edema, dilatation of the left ventricle and auricle, accentuation of the pulmonic second sound, the systolic murmur of relative mitral insufficiency, gallop rhythm, fall in arterial pressure and, rarely, alternation of the pulse. On the other hand, engorgement of the systemic veins, swelling of the liver, dependent edema and other manifestations of insufficiency of the right side of the heart are absent.

The characteristic clinical picture of isolated failure of the left side of the heart is encountered only when the functional capacity of the right ventricle is adequate to master the increased resistance in the pulmonary circuit that results from insufficiency of the left side of the heart. The dynamics of the circulation are then so altered that the pressure in the systemic veins is unchanged despite the engorgement of the lesser circulation. The negative characteristic of isolated failure of the left side of the heart, the absence of engorgement of the systemic veins, is readily demonstrated by direct measurement of the pressure in a superficial vein. Unfortunately however, no method is available for measuring in man the blood pressure in any portion of the pulmonary

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From the medical service and laboratories of the Mount Sinai Hospital

The investigation was aided by a grant to the Emanuel Libman Fellowship Fund in memory of Adele Schiff

1 White, P. D. Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle, *J. A. M. A.* **100** 1993 (June 24) 1933

2 Weiss, S., and Robb, G. P. Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and Syndrome of Left Ventricular Failure, *J. A. M. A.* **100** 1841 (June 10) 1933

circuit It is true that marked elevation in pressure in the pulmonary circuit can generally be inferred from the clinical symptoms already enumerated But there are also many cases in which the clinical evidence of pulmonary engorgement are obscure and lead to diagnostic difficulties For instance, one is not rarely in doubt whether paroxysmal dyspnea in a middle-aged or elderly person is due to bronchial asthma or results from left ventricular failure in coronary arteriosclerosis (cardiac asthma) Another occasional dilemma is to determine whether dyspnea and thoracic pain indicate mediastinal tumor or are correlated with arteriosclerotic heart disease

Lacking methods for measurement of the pressure within the pulmonary circuit, other means must be invoked to aid in the recognition of pulmonary engorgement when the usual clinical evidences are obscure One is the measurement of the circulation time along a pathway which includes the pulmonary circuit Since the pulmonary engorgement of failure of the left side of the heart is a passive congestion, it would appear a priori that there should be a tendency to a retardation of the blood flow through the lungs, with corresponding prolongation of the circulation time along any pathway which includes the pulmonary circuit That this is actually the case is indicated by the observation of Blumgart and Weiss<sup>3</sup> and Tarr, Oppenheimer and Sager,<sup>4</sup> who observed prolongation of the circulation time in various diseases marked by the type of circulatory disturbance here termed failure of the left side of the heart

In the following, we present data on the circulation time and venous pressure in failure of the left side of the heart by methods which are easily carried out and thus facilitate the recognition of failure of the left side of the heart in clinical work, not only in the hospital but also by the practitioner without laboratory facilities

#### METHODS

*Arm-to-Tongue Circulation Time*—The arm-to-tongue circulation time was measured by the interval elapsing between the injection of gluside into an antecubital vein and the perception of the sweet taste in the tongue (Fishberg, Hitzig and King<sup>5</sup>) By this technic, the arm-to-tongue circulation time in health is between nine and sixteen seconds

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3 Blumgart, H L, and Weiss, S The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardio-Vascular Disease, *J Clin Investigation* 5 343, 1928

4 Tarr, L, Oppenheimer, B S, and Sager, R V The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am Heart J* 8 766, 1933

5 Fishberg, A M Hitzig, W M, and King, F H Measurement of Circulation Time with Saccharin, *Proc Soc Exper Biol & Med* 30 651, 1933

*Arm-to-Lung Circulation Time*—This is measured by a method described by Hitzig<sup>6</sup> Five minims of ether mixed with an equal volume of physiologic solution of sodium chloride is injected into an antecubital vein, and the time elapsing until the ether vapor in the expired air is perceived by the subject and an observer is noted The interval is a measure of the circulation time between the antecubital vein and the arterial capillaries of the lung, which in health, varies between four and eight seconds

*Venous Pressure*—This was measured in an antecubital vein by a slight modification of the method of Taylor, Thomas and Schleiter<sup>7</sup> The manometer is an L-shaped tube of glass, to the short limb of which a 19-gage needle is attached The tube is moistened with a 10 per cent solution of sodium citrate The arm is supported, so that the vein is at the level of the right auricle The needle is introduced into the vein The height to which the blood rises<sup>1</sup> in the vertical limb of the tube indicates the venous pressure The details of the method were given elsewhere by Fishberg, Hitzig and King<sup>8</sup> In health, the venous pressure is between 4 and 8 cm of blood

#### CIRCULATION TIME

The arm-to-tongue circulation time is measured along the pathway from a large antecubital vein to the arterial capillaries of the tongue In table 1 are listed the arm-to-tongue circulation time and the venous pressure of thirty-one patients presenting the clinical picture of severe failure of the left side of the heart, as described previously It will be noted that the arm-to-tongue circulation time is markedly prolonged in all but the last patient, and even in this one it was above the upper limit of normal on one occasion The cases listed in the table are representative of our general observation, on over eight hundred patients in whom we have measured the arm-to-tongue circulation time, that the vast majority of persons with well marked symptoms of failure of the left side of the heart have prolonged arm-to-tongue circulation time Indeed, in some cases the arm-to-tongue circulation time is more than triple the normal time In order to evaluate the significance of this prolongation, it is necessary to consider individually the component pathways of the circuit traversed by the gluside

1 The first is the venous pathway from the antecubital vein to the right side of the heart The fact that the venous pressure is normal indicates that little of the prolongation of the circulation time is attributable to slowing of the blood flow in the large veins, for when heart failure results in stasis in the systemic veins, the pressure in the antecubital vein rises And the fact that the arterial pressure was not

6 Hitzig, W M Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries Proc Soc Exper Biol & Med **31** 935, 1934

7 Taylor, F A, Thomas, A B, and Schleiter, H G Direct Method for Estimation of Venous Pressure, Proc Soc Exper Biol & Med **27** 867, 1930

8 Fishberg, A M, Hitzig, W M, and King, F H Circulatory Dynamics in Myocardial Infarction, Arch Int Med **54** 997 (Dec) 1934

depressed in most of our patients indicates that diminished vis a teigo can hardly come into play as a cause of slowing of the blood flow in the veins, even though the volume output of the heart is doubtless

TABLE 1—*Venous Pressure and Arm-to-Tongue Circulation Time in Failure of the Left Side of the Heart*

Diagnosis	Venous Pressure, Cm of Blood	Arm to Tongue Circulation Time, Seconds
Essential hypertension, coronary arteriosclerosis	6	30
Essential hypertension, coronary arteriosclerosis	4	30
After digitalization	5	18 5
Essential hypertension in a malignant phase	7	38
Essential hypertension in a malignant phase	5 5	37
Essential hypertension in a malignant phase	5	30
	5 5	30
Coronary arteriosclerosis with myocardial damage	8	33
After digitalization	5	18
Coronary arteriosclerosis with myocardial damage	3	35
Coronary arteriosclerosis with myocardial damage	7	27
Coronary thrombosis	8	42
	6 5	36
Coronary thrombosis	4 5	32
Coronary thrombosis	3	33 5
Coronary thrombosis	4 5	38
Coronary thrombosis	6	29
	5 5	34
Coronary thrombosis	8 5	40
	8	39
	5 5	42
	7 5	35 75
Coronary thrombosis	3 5	51 75
	6 5	60 5
	7 5	39
Coronary thrombosis	7 5	35 5
Acute glomerulonephritis with pulmonary edema	6	28
Chronic glomerulonephritis	4	30
Syphilitic aortitis, aortic insufficiency	4	37
Syphilitic aortitis, aortic insufficiency	6 5	25 5
Syphilitic aortitis, aortic insufficiency	5 5	26 75
Syphilitic aortitis, aortic insufficiency	7 5	45 5
Syphilitic aortitis, aortic insufficiency	7 5	23 5
Mitral insufficiency and stenosis	6	30
Mitral insufficiency and stenosis	8	34
Mitral insufficiency and stenosis, aortic insufficiency	3	55
Aortic insufficiency, subacute bacterial endocarditis	6 5	30
Old rheumatic disease of aortic, mitral and tricuspid valves, subacute bacterial endocarditis	6 5	23
Heart block of undetermined origin	7 5	48
	6	44
	4 5	38 75
Arteriovenous aneurysm (popliteal) before operation	4	32
24 hours after operative obliteration of fistula	5	13
Hypertensive heart disease nephritis (?) essential (?)	5	11 25
	8 5	19
	8 5	13 75

diminished in many instances. Theoretical considerations thus indicate that retardation of the blood flow in the large systemic veins is not responsible for the prolongation of the arm-to-tongue circulation time in persons with isolated failure of the left side of the heart. Observations made by the radium C method, described by Blumgart and Weiss,<sup>3</sup> are in accord with these inferences. In patients with syphilitic heart



disease, suffering from what was evidently left ventricular failure, they found relatively little slowing of the blood flow between the antecubital vein and the right side of the heart

After the first draft of this paper had been completed, we were able to obtain direct evidence that in many instances of failure of the left side of the heart there is no slowing of the blood flow in the large systemic veins. The evidence is afforded by the results of measurements of the arm-to-lung circulation time by the ether method. This method affords a measure of the circulation time from the antecubital vein to the arterial capillaries of the lung. In table 2 are listed the arm-to-tongue (gluside) time, the arm-to-lung (ether) time and the venous pressure of seven patients with the typical and severe picture of isolated failure of the left side of the heart

TABLE 2—*Arm-to-Tongue and Arm-to-Lung Circulation Time and Venous Pressure in Failure of the Left Side of the Heart*

Diagnosis	Venous Pressure, Cm of Blood	Arm to Tongue Circulation Time, Seconds	Arm to Lung Circulation Time, Seconds
Coronary arteriosclerosis with myocardial damage	6	30 32	5 5 5
Coronary arteriosclerosis with myocardial damage	8	33 31	6 5
Hypertensive and arteriosclerotic heart disease	5 5	29	6 5
Mitral stenosis and insufficiency, aortic insufficiency	7	35	6 5
Mitral stenosis and insufficiency	5	24	5 75
Mitral stenosis and insufficiency	6 5	22 21	7 6 5
Syphilitic aortitis, aortic insufficiency	6	23	4 5

In these cases, the arm-to-lung circulation time was within normal limits despite the prolongation of the arm-to-tongue circulation time. This observation shows that in typical failure of the left side of the heart the prolongation of the arm-to-tongue circulation time is due entirely to slowing of the blood flow downstream to the arterial capillaries of the lung. We have also observed cases showing the clinical picture of failure of the left side of the heart in which the ether time as well as the gluside time was prolonged, in such instances, it is to be presumed that there is also some degree of insufficiency of the right side of the heart, although it is not sufficiently pronounced to result in elevation of the pressure in the systemic veins.

2 The second component is the pulmonary pathway from the right to the left side of the heart. The evidence is strong that almost all the prolongation of the arm-to-tongue circulation time observed in patients with failure of the left side of the heart is due to slowing of the blood flow through the lungs. The clinical features of failure of the left side of the heart listed earlier point unequivocally to the stasis of

blood in the pulmonary vessels. The roentgenographic appearance of the pulmonary vessels at the hilus and in the lung fields leaves no doubt that they are distended with blood in marked insufficiency of the left side of the heart. This distention results in an increase in the aggregate cross-section of the pulmonary vascular bed along its entire length. With such an increase in cross-section of the stream bed, a correspondingly decreased velocity of blood flow serves to transport the same volume of blood per minute from the right to the left side of the heart. Further, from the previous observations with the ether method, the conclusion can be drawn that the slowing of the blood flow is almost entirely in that portion of the pulmonary circuit downstream to the arterial capillaries.

3 The third component is the arterial pathway from the left side of the heart to the tongue. The time required to traverse the arterial pathway is doubtless very small in comparison with the total arm-to-tongue circulation time. We do not know how long a time elapses after the glucose has reached the arterial capillaries of the tongue before the taste buds are stimulated, but there seems no reason to believe that the time is prolonged by circulatory failure.

All in all, it appears justified to conclude that in patients with the clinical picture of failure of the left side of the heart and normal venous pressure the prolongation of the arm-to-tongue circulation time is due almost entirely to slowing of the blood flow through that portion of the pulmonary circuit downstream to the arterial capillaries.

It is to be emphasized that we found no strict parallelism between the prolongation of the arm-to-tongue circulation time and the intensity of the dyspnea and other symptoms of failure of the left side of the heart. To a large extent, such discrepancies seem to be attributable to the fact that there is no constant relationship between the pressure in the pulmonary circuit and the velocity of blood flow through it. The experimental investigations of von Basch,<sup>9</sup> Drinker, Peabody and Blumgart<sup>10</sup> and others have shown that an increase in pressure in the pulmonary circuit is an important factor in producing dyspnea, diminution in vital capacity and other symptoms of failure of the left side of the heart. The pressure in the pulmonary circuit is determined not only by the efficiency of the left ventricle and the capacity of the stream bed, but also by the volume of blood pumped into the pulmonary artery by the right side of the heart. The latter is decreased under two circumstances which are important in the present connection.

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<sup>9</sup> von Basch, S. *Klinische und experimentelle Untersuchungen*, Berlin, A. Hirschwald, 1891, vol. 1, p. 53.

<sup>10</sup> Drinker, C. E., Peabody, F. W., and Blumgart, H. L. The Effect of Pulmonary Congestion on the Ventilation of the Lungs, *J. Exper. Med.* **35** 77, 1922.

1 The first is the diminution in the venous return to the right side of the heart which occurs in different varieties of shock. The right side of the heart can pump no more blood into the pulmonary circuit than it receives from the systemic veins. The result is that in the presence of shock marked functional impairment of the left ventricle may not be accompanied by engorgement of the pulmonary circuit, because the return to the heart is so greatly diminished that it is within the capacity of even the severely damaged left ventricle. The classic example of such a state of affairs occurs in some instances of coronary thrombosis in which shock so decreases the venous return to the heart that symptoms of left ventricular failure are absent, despite a large infarct in the left ventricle.

2 When the right side of the heart fails, pulmonary engorgement is diminished, with alleviation of preexistent symptoms of failure of the left side of the heart despite the fact that the circulation time is even more protracted than previously. This is exemplified in the old observation that intensely orthopneic patients with aortic or coronary disease or hypertension may become much less dyspneic and orthopnea may regress with the appearance of such evidences of insufficiency of the right side of the heart as dependent edema and swelling of the liver.

There are also instances of isolated insufficiency of the left side of the heart in which the subjective symptoms are minimal—merely dyspnea on exertion elicited only by pointed questioning—and yet the circulation time is markedly prolonged. Indeed, in such cases the measurement of the circulation time may be the only available means of unveiling the weakness of the left ventricle. Excellent examples of this phenomenon were encountered in patients with malignant hypertension who entered the hospital with a circulation time of thirty-five seconds or more, although they complained only of headache, visual disturbances, uremic manifestations or other symptoms not correlated with heart failure.

*Failure of the Left Side of the Heart with Normal Circulation Time*  
—In exceptional instances, the arm-to-tongue circulation time is not prolonged despite the presence of severe symptoms of failure of the left side of the heart. An example of the few cases of this type that we have encountered is the last one in table 1. This patient, with high blood pressure, had severe orthopnea, and a roentgenogram revealed intense engorgement of the lungs. Nevertheless, the arm-to-tongue circulation time was normal on two occasions and only slightly prolonged on a third measurement. The explanation would seem to be that the right ventricle is sufficiently powerful to maintain a normal velocity of the blood flow through the lungs despite the increased resistance due to the insufficiency of the left side of the heart. However, the tension in

the pulmonary circuit is increased, with resultant dyspnea and other symptoms attributable to the hypertension of the lesser circulation

*Effect of Digitalis*—We have made a number of observations which revealed that when digitalization alleviates the subjective symptoms of failure of the left side of the heart, this is evidenced objectively by diminution in the arm-to-tongue circulation time. Two such cases are listed in table 1. This observation is of interest because it furnishes additional objective evidence that digitalis may be beneficial in isolated insufficiency of the left side of the heart with normal rhythm. Although the therapeutic value of digitalis in such cases has been doubted by some clinicians, including one of us (A M F), it has been especially affirmed by Harrison, Calhoun and Turley<sup>11</sup> on the basis of clinical observations. We have, however, observed in a number of instances of combined failure of the left and right sides of the heart that while digitalization brought the venous pressure down to normal, the reduction in circulation time was not equally pronounced, so that this still remained abnormally long.

#### VENOUS PRESSURE

The pressure in the peripheral veins is normal in isolated failure of the left side of the heart (table 1). Normal venous pressure is present in even very severe isolated failure of the left side of the heart. Thus, in a patient who had acute pulmonary edema due to left ventricular failure in glomerulonephritis with hypertension, the venous pressure was but 6 cm in the presence of a circulation time of twenty-eight seconds. We have made several similar observations. It is only when the right ventricle also gives way that any considerable elevation of venous pressure develops. However, in patients with an otherwise typical clinical picture of isolated failure of the left side of the heart, the following is to be borne in mind concerning slight elevation in the venous pressure to 9 or 10 cm. The right ventricle performs increased work because of the pulmonary hypertension due to failure of the left side of the heart. In accord with Starling's law, the right ventricle can perform this increased work only by means of greater diastolic filling and higher diastolic intraventricular tension, the latter of which is reflected in the venous pressure. It is therefore probable that slight elevation in venous pressure in the presence of failure of the left side of the heart does not per se indicate marked functional impairment of the right ventricle, but is simply a manifestation of the mechanism by which the right ventricle accommodates itself to the increased work necessitated by the

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11 Harrison, T R, Calhoun, J A, and Turley, F C. Congestive Heart Failure, Effect of Digitalis on Dyspnea and on Ventilation of Ambulatory Patients with Regular Cardiac Rhythm, Arch Int Med 48 1203 (Dec) 1931

pulmonary hypertension This is perhaps also the explanation of the slight enlargement of the liver that occasionally persists unchanged for months in patients with otherwise characteristic signs of failure of the left side of the heart

Increase in systemic venous pressure has been considered by some as an indicator of all forms of heart failure Thus Eyster<sup>12</sup> stated that 'a sustained rise of general venous pressure above the upper normal limit under basal conditions invariably accompanies cardiac decompensation' The normal venous pressure in failure of the left side of the heart obviously renders this view untenable for isolated insufficiency of the left side of the heart is a common form of cardiac decompensation and one which may last for years Only when the right ventricle also fails does the venous pressure rise

#### SUMMARY

In isolated failure of the left side of the heart the arm-to-tongue circulation time is almost always prolonged sometimes to three times the normal value

On the other hand, the arm-to-lung circulation time may be normal in failure of the left side of the heart despite markedly prolonged arm-to-tongue circulation time This shows that the prolongation of the arm-to-tongue circulation time in these cases is due to slowing of the pulmonary blood flow downstream to the arterial capillaries of the lung

The prolongation of the arm-to-tongue circulation time does not always parallel the severity of the other symptoms of failure of the left side of the heart In exceptional cases, the arm-to-tongue circulation time is within normal limits despite severe symptoms of failure of the left side of the heart

The circulation time in failure of the left side of the heart with normal rhythm may be shortened by digitalization, furnishing further objective evidence of the utility of digitalis in many patients with this circulatory disturbance

The systemic venous pressure is normal in isolated failure of the left side of the heart

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12 Eyster J A E Venous Pressure J A M A 97:1269 (Oct 31) 1931

# BLOOD FAT TOLERANCE TESTS IN MALNUTRITION AND OBESITY

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I have become interested in the problem of the regulation of fat as the result of treating nondiabetic malnourished patients with insulin. When such patients are made to gain weight rapidly, fat is deposited in the subcutaneous tissues to a noteworthy degree. This is a curious fact and suggests the possibility that insulin may have an effect on the metabolism of fat as well as on the metabolism of sugar.

## PLAN OF STUDY

An attempt was made to study fat tolerance in much the same manner that dextrose tolerance is customarily studied. A dose of 100 Gm of fat in the form of 500 cc of 20 per cent cream was employed as a test meal. This proved to be a reasonably palatable mixture, easily taken, and it never caused nausea, vomiting or diarrhea. It was administered to the patients in the morning after fasting over night. The plasma cholesterol was used as an indicator of the concentration of blood fat, because this analysis of the blood fats is the easiest to determine accurately and because, according to Joslin,<sup>1</sup> its percentage in plasma varies fairly consistently with the total amount of blood fat. In a number of cases the concentration of blood cholesterol was compared with that of the cholesterol ester, which has been shown by Knudson<sup>2</sup> to parallel the total blood lipid following the ingestion of fat. Since the cholesterol and cholesterol esters ran hand in hand, determinations of the latter were not used as a routine procedure.

The analyses were made on 2 cc samples of plasma, according to the method adopted by Bloor.<sup>3</sup> The tests<sup>4</sup> were made in duplicate, and all specimens obtained during a given test were read against the same standard. Samples of blood were obtained after fasting and two, four, six and eight hours after the fat meal was ingested, the patients remaining at rest during the interval and without additional food.

## OBSERVATIONS ON THE BLOOD FAT TOLERANCE CURVE

*In Normal Persons*—Fat tolerance tests were obtained in thirteen normal persons. The results are given in table 1.

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From the Medical Clinic of the Peter Bent Brigham Hospital

1 Joslin, E. P. Fat and the Diabetic, *New England J. Med.* **209** 519, 1933

2 Knudson, A. Relationship Between Cholesterol and Cholesterol Esters in the Blood During Fat Absorption, *J. Biol. Chem.* **32** 337, 1917

3 Bloor, W. R. The Determination of Small Amounts of Lipid in Blood Plasma, *J. Biol. Chem.* **77** 53, 1928

4 Miss Honora F. Carroll gave technical assistance

There was variation in the plasma cholesterol level after fasting, but comparatively little change was encountered as the result of the fat meal. The striking feature in normal people is the flatness of the cholesterol curve resulting from the ingestion of a fat meal. Rony and Levy<sup>5</sup> and Chaikoff, McGavack and Kaplan<sup>6</sup> also noted that the plasma cholesterol concentration in normal people is not affected by a fat meal.

TABLE 1—*Fat Tolerance Tests in Normal People*

Case	Plasma Cholesterol Levels, Mg per 100 Cc of Blood Plasma				
	Fasting	Hours After Test Meal*			
		2	4	6	8
1	204	195	195	191	223
2	187	195	180	182	182
3	223	218	237	204	205
4	204	218	213	215	188
5	195	223	215	213	201
6	201	205	210	208	203
7	189	193	187	189	185
8	203	210	203	197	191
9	171	178	191	185	183
10	240	253	246	240	234
11	169	171	182	173	169
12	176	187	167	161	156
13	231	240	246	228	213
Average	199	207	206	199	195

\* This consisted of 500 cc of 20 per cent cream

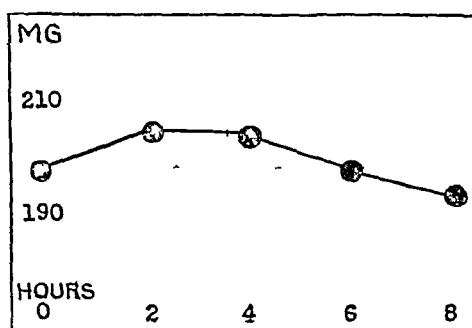


Chart 1—Average plasma cholesterol curve obtained in thirteen normal persons after a test meal of 100 Gm of fat. In all the charts the cholesterol is recorded in milligrams per hundred cubic centimeters of plasma and the time interval in hours.

*In Malnutrition*—Fat tolerance tests were obtained in sixteen persons, who were very thin but otherwise normal, before or after and

5 Rony, H R, and Levy, A J. Fat Tolerance in Obesity, *J Lab & Clin Med* **15** 221, 1929

6 Chaikoff, I L, McGavack, T H, and Kaplan, A. The Blood Lipids in the Post Absorptive State and After the Ingestion of Fat in Normal Human Subjects and in a Case of Disseminated Cutaneous Xanthomata, *J Clin Investigation* **13** 1, 1934

during a period of administration of insulin. In the cases studied during the period of treatment with insulin, 10 units of insulin was injected subcutaneously three times a day for a period before the test was made. In the cases studied after the discontinuation of insulin, at least a week was allowed to elapse before the final test was made. The results of the various tests are given in table 2.

TABLE 2—*Fat Tolerance Tests in Malnourished People With and Without Insulin*

Case	Plasma Cholesterol Levels Without Insulin, Mg per 100 Cc of Blood Plasma					Length of Time After Omitting Insulin	Plasma Cholesterol Levels With Insulin, Mg per 100 Cc of Blood Plasma					Period of Insulin Therapy
	Fast- ing	Hours After Test Meal*					Fast ing	Hours After Test Meal*				
		2	4	6	8			2	4	6	8	
1	157	146	139	145	128	4 months	206	237	203	197	203	2 weeks
2	152	141	139	147	156	1 week	187	198	220	160	183	6 months
3	172	176	184	167	164	3 months	199	177	166	223	166	1 week
4	199	183	193	201	203	1 week	225	234	257	231	228	7 months
5	227	206	197	193	193	2 weeks	203	219	224	202	196	2 months
6	267	272	259	250	237	2 years	215	247	254	228	206	9 days
7	197	234	243	223	220	5 months	220	238	250	260	208	10 days
8	187	192	163	158	156	8 months	208	229	240	211	205	1 week
9	213	223	210	195	191	8 days	164	183	187	171	153	2 weeks
10	190	200	178	180	176	Before insulin	208	257	264	223	206	2 weeks
11	220	225	231	228	213	Before insulin	191	208	215	259	201	1 week
12	184	203	178	182	188	Before insulin	178	186	192	204	182	3 weeks
13	172	142	168	170	153	Before insulin	178	195	180	165	161	8 days
14	234	237	223	218	215	Before insulin	191	195	205	201	189	2 weeks
15	215	225	220	199	197	Before insulin	223	237	246	240	225	2 months
16	199	195	193	187	178	Before insulin	216	241	251	226	210	3 weeks
Aver	199	200	195	190	185		201	217	222	212	195	

\* This consisted of 500 cc of 20 per cent cream

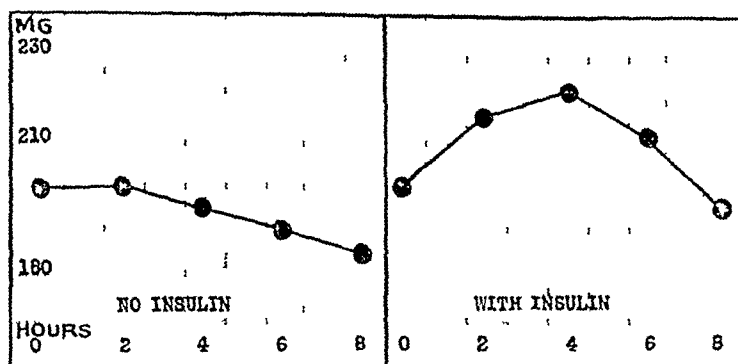


Chart 2—Average plasma cholesterol curves obtained in sixteen thin people following the fat meal, before or after and during a period of treatment with insulin

As in the strictly normal group, there was more or less variation in the plasma cholesterol level after fasting during the various periods of observation, but the average curve noted following the fat meal without insulin was much as in the normal person. In certain cases there appeared to be a less than normal rise in the curve and a sharper than



normal fall, suggesting either deficient absorption of the fat meal or its more rapid passage through the blood

The curves for plasma cholesterol obtained during the period of administration of insulin were strikingly different. Here the plasma cholesterol concentration rose sharply and remained elevated for several hours after the ingestion of the cream, decreasing to near the fasting level at the end of the period of observation. These results do not confirm the experimental work on dogs by Rony and Ching,<sup>7</sup> who found that insulin inhibits alimentary lipemia, of White,<sup>8</sup> who showed that insulin has no constant effect on the blood cholesterol level, or of Christomanos,<sup>9</sup> who believed that insulin lowers the serum fat level of normal subjects.

*In Obesity*—It was of interest to compare the cholesterol curves obtained in thin people fattening under insulin therapy with the curves

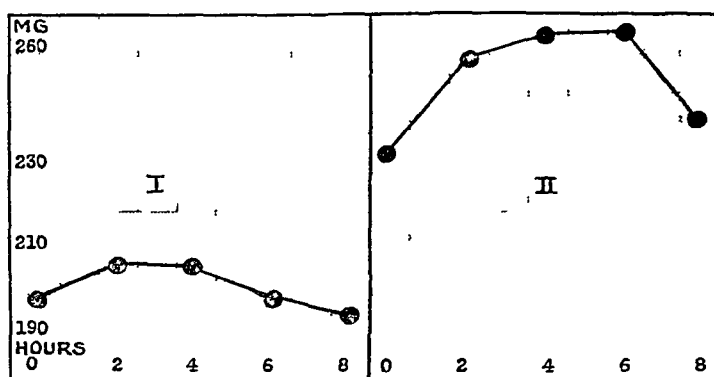


Chart 3—Comparison of average plasma cholesterol curves obtained in thirteen normal (I) and twenty-one obese (II) people after the test meal of 100 Gm of fat

normally obtained in untreated obese persons. For this purpose a group of twenty-one patients who were considerably overweight for their height, age and sex were selected. The weights of these subjects ranged from 131 to 275 pounds (59.4 to 124.7 Kg), and each was at least 20 pounds (9.1 Kg) over standard weight for age, sex and height, many being from 50 to 117 pounds (22.7 to 53.1 Kg) overweight. The results of the tests are given in table 3.

There was considerable variation encountered in the plasma cholesterol level after fasting, many of the group having after fasting hypercholesteremia of varying degree. After the test meal there was likely to be a marked rise in the cholesterol curve which persisted for several hours, tending to return to near the level of fasting toward

7 Rony, H. R., and Ching, T. T. Effect of Insulin on Alimentary Lipemia in Normal Dogs, *Proc Soc Exper Biol & Med* **27** 533, 1930.

8 White, A. C. Insulin and the Blood Fat, *Biochem J* **19** 921, 1925.

9 Christomanos, A. A. Ueber den Einfluss des Insulins auf die Fettverteilung im Serum, *Biochem Ztschr* **214** 482, 1929.

the end of the period of observation. The curves were strikingly similar to those obtained in thin people during a period of insulin therapy.

*Effect of Extract of Pituitary in Obesity*—In a series of experiments carried out on dogs, Raab<sup>10</sup> demonstrated that extract of pituitary causes the blood fat level to fall. His observation may be accounted for in part by the marked increase in fatty acids in the liver which Coope and Chamberlain<sup>11</sup> showed are laid down in animals following the administration of extract of pituitary. Raab's experiments are

TABLE 3—Fat Tolerance Tests in Obese Patients

Case	Plasma Cholesterol Levels, Mg per 100 Cc of Blood Plasma					Weight, Pounds	Over weight, Pounds
	Fast ing	Hours After Test Meal*					
		2	4	6	8		
1	189	220	312	246	217	170	25
2	203	218	220	254	208	226	48
3	250	275	288	272	237	250	92
4	456	492	506	526	506	204	71
5	234	257	293	237	231	211	73
6	234	279	297	275	263	200	47
7	201	231	240	312	263	131	26
8	228	254	261	260	206	161	36
9	218	228	263	243	225	180	28
10	249	312	318	328	263	170	20
11	213	228	237	225	210	255	115
12	220	237	246	237	225	220	90
13	183	183	171	178	176	224	74
14	328	367		360	307	142	22
15	220	237	240	231	243	162	36
16	220	228	228	215	215	236	66
17	225	234	240	260	243	212	60
18	215	228	231	225	228	275	117
19	197	203	215	220	208	243	115
20	234	253	263	246	246	215	75
21	218	243	218	225	208	200	50
Average	235	258	264	265	244		

\* This consisted of 500 cc of 20 per cent cream

convincing and suggest that the pituitary gland plays an important part in the regulation of fat metabolism. Since marked changes in the cholesterol level after a fat test meal were obtained in obese people, it seemed of interest to determine whether extract of pituitary could demonstrably change the reactions and produce results like those described by Raab.

Fat tolerance tests were made in nine obese patients on one day without the administration of extract of pituitary and then several days later after they had received extract of pituitary. The preparation was admin-

10 Raab, W. The Rôle of the Pituitary Posterior Hormone in Fat Metabolism, *Endocrinology* **14**:385, 1930

11 Coope, R., and Chamberlain, E. N. The Effect of Pituitrin on the Fatty Acid of the Liver, *J. Physiol.* **60**: 69, 1925

istered intranasally, according to Blumgart's method<sup>12</sup> for treating diabetes insipidus. A small piece of cotton was soaked in extract of the posterior lobe of the pituitary of obstetric strength so that about 1 cc of the solution was absorbed. Immediately after the ingestion of the cream the cotton pledget was placed in a nostril just above the middle turbinate and was left in place, being refreshed every two hours, just after the specimens of blood were taken. Such a procedure allowed continuous absorption of the extract of pituitary over a long period of time. In a few cases

TABLE 4—*Fat Tolerance in Obese Patients Taking Extract of Pituitary*

Case	Plasma Cholesterol Levels, Mg per 100 Cc of Blood Plasma									
	No Pituitary Administered					Pituitary Administered*				
	Fasting	Hours After Test Meal†				Fasting	Hours After Test Meal†			
		2	4	6	8		2	4	6	8
1	201	231	240	312	263	206	205	203	214	199
2	249	312	318	328	263	223	234	228	228	225
3	213	228	237	225	210	205	208	197	203	203
4	220	237	240	231	243	223	220	208	201	195
5	220	228	228	215	215	213	203	201	210	208
6	436	492	506	526	206	323	353	360	328	347
7	215	228	231	225	228	228	215	228	218	218
8	234	279	297	275	263	210	225	234	231	228
9	197	203	215	220	208	208	197	193	195	195
Average	245	271	279	284	233	227	229	228	225	224

\* Extract of pituitary was administered intranasally immediately after each specimen of blood was taken.

† This consisted of 500 cc of 20 per cent cream.

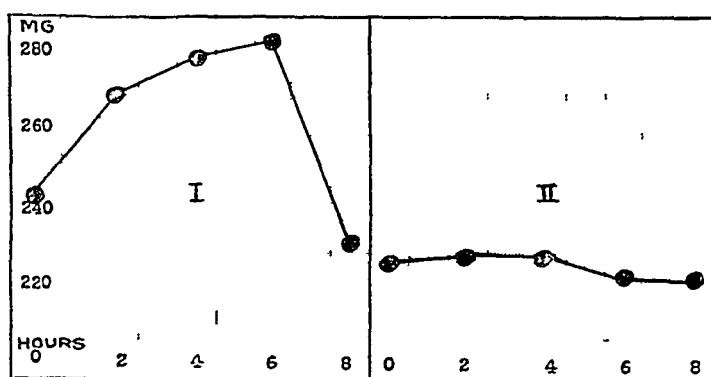


Chart 4—Average plasma cholesterol curves obtained in nine obese persons following the test meal of 100 Gm of fat, with (II) and without (I) administration of extract of pituitary.

0.5 or 1 cc of the extract was administered intramuscularly every two hours, but as the results obtained by the intranasal method of administration were practically identical with those obtained when the drug was administered hypodermically, the latter method was discontinued because of the discomfort involved. The results of the tests are given in table 4.

12 Blumgart, H. L. Diabetes Insipidus with Particular Reference to Further Experience with Treatment by Pituitary Posterior Lobe Extract Applied Intranasally, *M. Clin. North America* **15**: 895, 1932.

There was a typical rise in the plasma cholesterol level in the obese patients as the result of the fat meal, but when extract of pituitary also was administered, comparatively little variation in the plasma cholesterol concentration was encountered. Extract of pituitary appeared to prevent a significant rise in the cholesterol level and in a few instances seemed actually to cause a decrease in the cholesterol level below the concentration after fasting, so that the resultant curves were similar to those found in certain of the normal thin subjects.

TABLE 5—*Fat Tolerance in Patients with Diabetes Insipidus Taking Extract of Pituitary*

Case	Plasma Cholesterol Levels, Mg per 100 Cc of Blood Plasma									
	No Pituitary Administered					Pituitary Administered*				
	Fasting	Hours After Test Meal†				Fasting	Hours After Test Meal†			
		2	4	6	8		2	4	6	8
1	256	289	308	318	358	238	250	264	264	240
2	240	249	263	271	297	240	243	243	253	240
3	187	195	223	234	231	180	189	185	168	171
4	187	195	205	215	199	187	183	180	185	191
5	201	215	225	228	237	208	201	205	197	187
6	201	213	234	228	225	195	201	205	191	191
7	234	257	220	225	228	234	208	205	201	166
Average	215	230	240	246	254	212	211	212	208	198

\* Extract of pituitary was administered intranasally immediately after each specimen of blood was taken.

† This consisted of 500 cc of 20 per cent cream.

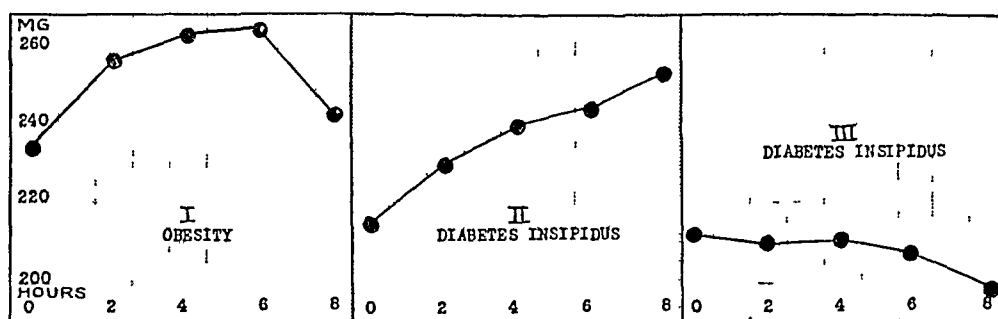


Chart 5—Comparison of average plasma cholesterol curves obtained following the test meal of 100 Gm of fat in seven patients with diabetes insipidus, with (III) and without (II) administration of extract of pituitary and in twenty-one obese persons who did not receive treatment (I).

*Extract of Pituitary in Diabetes Insipidus*—These observations were so striking that finally it appeared logical to test the fat tolerance of certain persons known to have insufficiency of the pituitary gland. For this purpose seven patients with diabetes insipidus were studied. Although it may be argued that the tuber cinereum or other structures allied to the pituitary gland are at fault in this disease, nevertheless the administration of extract of pituitary admittedly relieves the symp-

toms of polyuria and excessive thirst in most cases. The results of the fat tolerance tests in this group are given in table 5.

Without extract of pituitary there was a marked rise of the plasma cholesterol concentration following the ingestion of cream, similar to that observed in the obese subjects. In cases 1, 2 and 5 the cholesterol level continued to rise during the entire eight hour period of observation. In no case did the cholesterol curve appear to depend on the patient's state of nutrition because certain of the patients were thin and none were remarkably fat. When extract of pituitary was administered after the ingestion of cream and at two hour intervals subsequently, the plasma cholesterol level was flattened, showing a normal type of reaction.

#### COMMENT

The proper explanation of the results obtained in this study is, at present, uncertain. Certainly these data suggest that both insulin and extract of pituitary modify appreciably the type of blood fat curves obtained after a fat meal, insulin causing a rise in blood fat concentration and extract of pituitary a fall. That insulin and extract of pituitary have antagonistic effects on the blood sugar level has already been pointed out by Burn<sup>13</sup> and Blotner and Fitz<sup>14</sup>. The data recorded here suggest that the two substances likewise influence the blood fat level and in opposite ways.

The appearance of an increase in the plasma cholesterol level following the administration of insulin and cream in thin people suggests that insulin may cause an increase in the rate of absorption of fat from the gastro-intestinal tract or possibly that, owing to the presence of insulin, the cholesterol is not removed from the blood as rapidly as usual. That insulin increases the absorption of food and dextrose has already been proposed by Koref and Mautner<sup>15</sup> and Blotner<sup>16</sup>.

The striking similarity between the fat tolerance curves obtained in obese persons and in thin people receiving insulin suggests the possibility that there may be available an increased amount of insulin in obesity, this accounting for the rise in the plasma cholesterol level which was noted following the ingestion of cream. If this assumption is cor-

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13 Burn, J. H. The Modification of the Action of Insulin by Pituitary Extract and Other Substances, *J. Physiol.* **57** 318, 1923.

14 Blotner, H., and Fitz, R. The Effect of Insulin, Pituitrin and Adrenalin on the Blood Sugar Level, *J. Clin. Investigation* **5** 51, 1927.

15 Koref, O., and Mautner, H. Zur Resorptionsbeschleunigung durch Insulin, *Klin. Wchnschr.* **5** 191, 1926.

16 Blotner, H. Observations on the Effect of Insulin in Thin Persons, *J. A. M. A.* **100** 88 (Jan 14) 1933, Insulin and Sugar Tolerance in Thin People, *Arch. Int. Med.* **53** 153 (Jan) 1934.

rect, it would explain satisfactorily the increased appetite so often met with in obese people

On the other hand, the results after the administration of extract of pituitary are equally striking. Extract of pituitary appears to decrease the plasma cholesterol concentration after a test meal of fat. This decrease in blood fat has been shown at least in part to be due to the deposit of fat in the liver by extract of pituitary. There is also the possibility that extract of pituitary acts on the intestines, inhibiting the absorption of fat. Finally, pituitary dysfunction may be the cause of obesity in certain persons, as has been suggested by Dercum,<sup>17</sup> Cushing<sup>18</sup> and others. Perhaps obesity in general is associated with varying degrees of pituitary insufficiency. Such an idea is supported to some extent by the similarity of cholesterol curves obtained after the ingestion of cream by patients with diabetes insipidus and by obese patients, both being influenced by the administration of extract of pituitary.

#### TREATMENT OF OBESITY WITH EXTRACT OF PITUITARY

Assuming from the results of the tests that in obesity there may be hypofunction of the pituitary gland, it appeared logical to apply this idea clinically in treatment. Consequently, an effort was made to determine whether obese persons could be made to lose weight with the administration of extract of pituitary and without any other form of treatment.

Extract of pituitary was administered intranasally three times a day after meals to a group of six obese people, the cotton pledget being retained in the nose for two hours after each application. No dietetic restrictions were advised, in fact, the patients were encouraged to eat normally and to take as much food as they desired. Although the series is small and the patients have been observed for but a short period of time, yet the immediate results appear to be of some interest. So far, in each case there has been an average loss of weight of from 1½ to 2 pounds (0.75 to 0.9 Kg.) a week under this management. The greatest amount of weight lost thus far by any one patient is 17 pounds (7.7 Kg.) in ten weeks. Obviously it will require a much longer period of time to test the efficacy of such a method of treatment of obesity.

#### SUMMARY AND CONCLUSIONS

This paper presents a study of alimentary fat tolerance, using the plasma cholesterol as an indicator of the blood fat concentration, and as a test meal 500 cc. of 20 per cent cream.

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17 Dercum, F. X., and McCarthy, D. J. Autopsy in a Case of Adiposa Dolorosa, *Am J M Sc* **124** 994, 1902.

18 Cushing, H. *The Pituitary Body and Its Disorders*, Philadelphia, J. B. Lippincott Company, 1912.

In normal persons the plasma cholesterol level following the ingestion of such a test meal remains practically unchanged during an eight hour period

In thin persons the cholesterol level after such a test meal remains unchanged or even shows a decrease. Under insulin therapy, however, there is a significant rise in the cholesterol level after such a test meal.

In obese persons there is a marked rise in the cholesterol level after such a test meal. The blood fat curve in obesity is similar to that obtained in malnourished people receiving insulin.

In diabetes insipidus after such a test meal the cholesterol level increases markedly, and the resultant curve is similar to that obtained in obesity.

Extract of pituitary administered intranasally modifies the plasma cholesterol curve obtained after a fat test meal in patients with obesity and diabetes insipidus. Extract of pituitary prevents the development of hyperlipemia which otherwise occurs.

Insulin and extract of pituitary have effects on fat as well as on sugar metabolism that are of opposite nature, insulin causing a rise in the blood fat concentration after a fat meal and extract of pituitary a fall.

In a group of six obese patients treated for short intervals with applications of extract of pituitary intranasally and without diet there has been an average weekly loss of from  $1\frac{1}{2}$  to 2 pounds. The greatest amount of weight lost under this form of therapy by any one patient has been 17 pounds in ten weeks. Although these results are of some interest, no definite conclusions can be drawn regarding their significance. The possibilities of such a method of treating obesity will remain uncertain until further studies have been completed.

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# SIGNIFICANCE OF THE PHENOLSULPHONPHTHALEIN TEST OF RENAL FUNCTION

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SAN FRANCISCO

The aim of any test of biologic function is to determine the existing function of an organ or tissue in relation to the function if the tissue or organ and organism as a whole were normal. A quantitative consideration is necessary for the proper evaluation of any function. In the case of the kidney, an attempt to measure the amount of functioning renal tissue must be the aim of any test of function. The test with phenolsulphonphthalein (phenol red) is probably the most widely used, at least in this country, of the numerous tests of renal function which have been proposed, and it is the purpose of the present study to inquire to what degree it meets the criteria. When the test was first described by Rowntree and Geraghty,<sup>1</sup> it was found experimentally that the removal of half the normal renal tissue was without influence on the results of the test. However, the idea has grown up that the normal excretion of the dye indicates unimpaired renal function, a conclusion which is obviously incorrect. We are unaware of any study in which a constant relation of the test to the functioning renal tissue has been demonstrated. The mode of excretion of the dye by the kidney is uncertain,<sup>2</sup> but there is evidence<sup>3</sup> that it is excreted in a manner similar to that of urea. On theoretical grounds it would therefore be surprising if consistent results were obtained with the phenol red test, as ordinarily performed, for the speed of excretion of an administered quantity of

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From the Scripps Metabolic Clinic, La Jolla, Calif, and the Department of Medicine, Stanford University School of Medicine, San Francisco

1 Rowntree, L G, and Geraghty, J T. An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonphthalein, *J Pharmacol & Exper Therap* **1** 579, 1910

2 Richards, A N. Methods and Results of Direct Investigations on the Functions of the Kidney, Baltimore, Williams & Wilkins Company, 1929  
Marshall, E K, Jr. The Secretion of Phenol Red by the Mammalian Kidney, *Am J Physiol* **99** 77, 1931

3 MacKay, E M, and Oliver, J. A Comparison of the Method of Excretion of Neutral Red and Phenol Red by the Mammalian Kidney, *J Exper Med* **51** 161, 1930



urea could give only the vaguest idea of the renal function. In several respects, however, the excretion of the dye is different. The dye is given intravenously, while urea is administered by mouth, hence the urea reaches the blood stream and becomes available to the kidney in an uncertain length of time. In determining the percentage of excretion of phenol red the base-line is zero, while with urea the base-line is a variable and uncertain level which is determined by a large number of factors. It is probably these differences which give the phenolsulphonphthalein test the value which it appears to have under certain conditions.

An attempt was first made to determine the relation between the percentage excretion of the dye and the size of the kidney in normal rabbits. Here, of course, it was necessary to vary the size of the kidney and of the entire organism together, a factor which may have been responsible for our failure to find any relationship. When 6 mg of dye was injected intravenously, small rabbits with relatively small kidneys were found to excrete practically as much during the ensuing two hours as large rabbits with larger renal organs. Likewise, there was no relation between the percentage of dye excreted and the weight of the kidneys when the dose of dye was made approximately the same as that for man (3 mg per square meter) on the basis of body surface or was increased to make allowance for the fact that the rabbit has about five times as much kidney as man in relation to body mass, when this is measured as body surface.

Observations on normal persons were equally unsatisfactory so far as a constant relation to the probable weight of the kidney was concerned. We have gained the impression that a relation between the percentage excretion of phenol red and renal weight may be demonstrated only when the body mass remains essentially constant, while the amount of functioning renal tissue is varied. This condition existed in a group of patients suffering from Bright's disease, in whom there were varying degrees of impairment of renal function. In this group the phenolsulphonphthalein test was compared with the amount of functioning renal tissue as measured by Addis' procedure.<sup>4</sup>

#### TEST OF RENAL FUNCTION

*The Phenolsulphonphthalein Test*—The dye test was carried out in the usual manner. There was no alteration in the patients' daily routine, and the test was generally performed in the morning. Fifteen minutes before the dye was given

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<sup>4</sup> Addis, T. Renal Function and the Amount of Functioning Tissue, Arch Int Med 30 378 (Sept) 1922

the patient received 400 cc of water. Fifteen minutes later the subject voided completely, and within two or three minutes 1 cc of the commercial dye solution containing 6 mg of the monosodium salt of phenolsulphonphthalein was injected intravenously from a tuberculin syringe. It is generally agreed that any other method of administration than the intravenous route gives inconsistent results, for the amount of dye which is actually available to the kidney is then an unknown quantity. Exactly one and two hours after the injection of the dye, complete samples of urine were collected, and the amount of dye excreted was determined by comparison in a Duboscq colorimeter with a standard solution prepared from the same lot of dye as that used for injection. If the excretion of dye proved to be higher in the second hour than in the first, the test was discarded, for this was considered evidence of an obstruction of the urinary tract or of retention in the bladder and consequently a false indication of the renal excretion of the dye.

*The Addis Test*—This test measures the amount of functioning renal tissue and depends on the determination under certain standard conditions of the ratio

$$\frac{\text{urine urea rate}}{\text{blood urea concentration}}$$
 The evidence that the procedure actually measures the amount of functioning renal tissue may be summarized briefly as follows. Considered as the volume of blood which is freed by the kidneys of urea per unit of time,<sup>5</sup> it is a reasonable measure of renal function. Under the standard conditions the ratio is remarkably constant for a given subject.<sup>6</sup> In normal rats,<sup>7</sup> rabbits<sup>8</sup> and dogs<sup>9</sup> the ratio bears a direct linear relationship to the actual weight of the kidneys. In rabbits with nephritis induced by uranium the renal function, as measured in this manner, has been shown<sup>10</sup> to vary with the amount of functioning renal tissue, as approximated anatomically. When half the renal tissue is removed by unilateral nephrectomy the ratio is cut in half,<sup>11</sup> and as compensatory hypertrophy of the remaining kidney ensues the ratio follows closely the development

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5 (a) Addis, T, and Watanabe, C K. A Method for the Measurement of the Urea Excreting Function of the Kidneys, *J Biol Chem* **28** 251, 1916. (b) Addis, T. The Renal Lesion in Bright's Disease, *Am J M Sc* **176** 623, 1928. (c) Addis, T, and Oliver, J. The Renal Lesion in Bright's Disease, New York, P B Hoeber, Inc, 1931.

6 Addis, T, and Drury, D R. The Rate of Urea Excretion. V The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, *J Biol Chem* **55** 105, 1923. Pollard, W S. The Effect of Some Diuretics on the Urea-Excreting Capacity of the Kidney, *Am J Physiol* **85** 141, 1928.

7 MacKay, E M, and Raulston, B O. Factors Which Determine Renal Weight. XI Renal Function, *J Exper Med* **53** 109, 1931.

8 Taylor, F B, Drury, D R, and Addis, T. The Relation Between the Rate of Urea Excretion and the Size of the Kidney, *Am J Physiol* **65** 55, 1923.

9 MacKay, E M. A Comparison of the Relation Between the Rate of Urea Excretion and the Amount of Renal Tissue in the Dog and Other Mammals, *Am J Physiol* **100** 402, 1932.

10 Watanabe, C D, Oliver, J, and Addis, T. Determination of the Quantity of Secreting Tissue in the Living Kidney, *J Exper Med* **28** 359, 1918.

11 Addis, T, Myers, B A, and Oliver, J. The Effect of Unilateral Nephrectomy on the Function and Structure of the Remaining Kidney, *Arch Int Med* **34** 243 (Aug) 1924.

of the hypertrophy as measured anatomically<sup>12</sup> In man the ratio is also proportional to the body surface, while the body surface and the weight of the kidneys are, in turn, in straight-line association<sup>13</sup>

The details of the Addis ratio test have already been described<sup>5c</sup> The normal value for the ratio,  $\frac{\text{urea in a one hour specimen of urine}}{\text{urea in 100 cc of blood}}$ , under the standard conditions is 277 per square meter of body surface<sup>14</sup> Our results are expressed as percentages of this normal value

*Data*—Our figures are based on one hundred and thirty-nine observations on eighty-two patients with Bright's disease The phenolsulphonphthalein and the Addis ratio test were made not longer than three days apart On the day before the measurement of the ratio the blood urea concentration was determined for comparison of its relation to the functioning renal tissue<sup>15</sup> with that of the phenolsulphonphthalein test

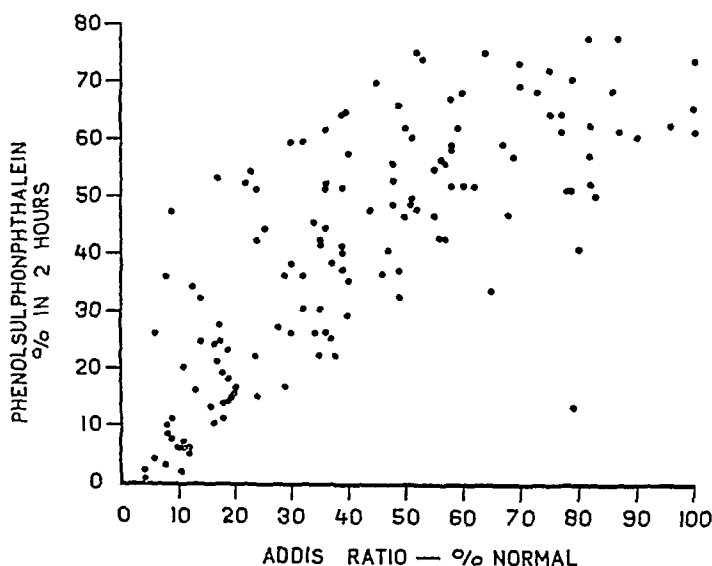


Chart 1—A scatter diagram showing the relation of the excretion of phenolsulphonphthalein to the Addis ratio

The results of the individual observations on the excretion of phenolsulphonphthalein are shown in the scatter diagram (chart 1) The picture is similar to that of the relation of the phenolsulphonphthalein test to the standard blood urea

12 Oliver, J The Regulation of Renal Activity X The Morphologic Study of the Effect of Unilateral Nephrectomy on the Function and Structure of the Remaining Kidney, Arch Int Med **34** 258 (Oct) 1924

13 MacKay, E M Kidney Weight, Body Size and Renal Function, Arch Int Med **50** 590 (Oct) 1932

14 Volhard, F, and Suter, F Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p 155 Addis and Oliver<sup>5c</sup> McKay<sup>13</sup>

15 MacKay, E M, and MacKay, L L The Relation Between the Blood Urea Concentration and the Amount of Functioning Renal Tissue, J Clin Investigation **4** 127, 1927

clearance test of Van Slyke<sup>16</sup> As with the blood urea concentration,<sup>15</sup> the normal values for phenolsulphonphthalein may be obtained until the renal function is reduced to less than half of normal

*Statistical Analysis*—One of us (D A R) has pointed out elsewhere<sup>17</sup> that it is possible by statistical analysis to determine the clinical value of tests of function, not only through their correlation, but also through the shape of their regression, with the amount of functioning tissue which it is designed to measure These factors seem equally important In the present instance it is known that the Addis ratio represents the functioning renal tissue The tests of excretion of

TABLE 1—*Statistical Characteristics of the Addis Ratio (per Cent of Normal) with Blood Urea Concentration and Excretion of Phenolsulphonphthalein*

Characteristics of Addis Ratio*	Phenolsulphonphthalein, per Cent Excreted in Two Hours	Blood Urea, Mg per 100 Cc
$\bar{x}$	$+0.757 \pm 0.024$	$-0.630 \pm 0.034$
$\frac{xy}{\sum PE \sum}$	$+0.749$	$-0.682$ $-2.38$
$\frac{y^2}{\sum PE \sum}$	$+0.791$ $2.04$	$-0.805$ $5.02$
$M_x$	$42.60 \pm 1.45$	$42.60 \pm 1.45$
$M_y$	$40.90 \pm 1.16$	$57.62 \pm 2.47$
$\sigma_x$	$25.29 \pm 1.02$	$25.29 \pm 1.02$
$\sigma_y$	$20.34 \pm 0.82$	$43.15 \pm 1.75$
N	139	139

\* The Addis ratio is denoted by  $x$  in each instance, the other variables by  $y$  The regression of the Addis ratio on the phenolsulphonphthalein excretion was  $x = 0.941y + 4.1$ , and the regression of phenolsulphonphthalein on the Addis ratio was  $y = 41.16 + 0.2315x - 42.93e^{-0.0478x}$  The relation of the Addis ratio and the blood urea concentration was  $xy = 1.755$

phenolsulphonphthalein and blood urea concentration are to be evaluated The statistical terms are described and a more complete description of the methods used is given elsewhere<sup>18</sup> In table 1 are presented the statistical characteristics of the observations under consideration Tables 2 and 3 are the correlation tables, with the regression data in the margins

16 Van Slyke, D, McIntosh, F T, Moller, E, Hannon, R R, and Johnston, C Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, *J Clin Investigation* **8** 363, 1930

17 Rytand, D A The Rate of Excretion of Urine in Subjects with Different Amounts of Renal Tissue, *J Clin Investigation* **11** 1153, 1933

18 Pearl, R Introduction to Medical Biometry and Statistics, ed 2, Philadelphia, W B Saunders Company, 1930 Rytand<sup>17</sup>

TABLE 2—The Correlation of the Addis Ratio and the Excretion of Phenolsulphonphthalein

Phenolsulphon phthalein, per Cent Excreted in Two Hours	Addis Ratio, per Cent of Normal																			Means Of Ratio
	0 4 9	5- 9 9	10 14 9	15 19 9	20- 24 9	25- 29 9	30 34 9	35- 39 9	40 44 9	45- 49 9	50 54 9	55 59 9	60 64 9	65- 69 9	70 74 9	75- 79 9	80 84 9	85 89 9	90 94 9	
75 to 79											2		1		1	1	1			73 10
70 to 74										2		1	1		2	1	1	1		68 25
65 to 69								3			1	1								
60 to 64											1	2					1	1	1	
55 to 59							2	3	1	2	1	4	2	2		1	1		1	
50 to 54				1	3															
45 to 49		1																		
40 to 44					1	1	1	5	1	1	4	1	2	1		1	1			
35 to 39		1					2	2	1	2										
30 to 34			2			1	1	1	1	1				1						
25 to 29		1		1		1	2	1	1											
20 to 24			2	4	1			3												
15 to 19			1	2	3	1										1				
10 to 14		2		6																
5 to 9		3	3																	
0 to 4	2	2	2																	
Total	2	10	10	14	8	4	8	18	4	9	8	11	4	4	3	8	6	3	1	4
Means of phenolsulphon phthalein	11 15		18 10		33 30		41 75		46 70		54 85		55 00		58 40		60 85		63 50	

TABLE 3—*The Correlation of the Addis Ratio and the Blood Urea Concentration*

Blood Urea, Mg per 100 Cc	Addis Ratio, per Cent of Normal																				Means of Ratio
	0 4.9	5 9.9	10 14.9	15 19.9	20 24.9	25 29.9	30 34.9	35 39.9	40 44.9	45 49.9	50 54.9	55 59.9	60 64.9	65 69.9	70 74.9	75 79.9	80 84.9	85- 89.9	90 94.9	95 99.9	
260 to 279	1																				1 2.50
240 to 259																					0
220 to 239																					0
200 to 219	1	1																			0
180 to 199		2																			2 5.00
160 to 179		1																			2 7.50
140 to 150		1																			1 7.50
120 to 139		1	1	1																	2 10.00
100 to 119		3	1	2	1																3 12.50
80 to 99			5	1	1																7 13.20
60 to 79		1	1	4	1		2	6	2		1		1								6 14.15
40 to 59			1	3	5	3	3	3	1	3	3	1	2	1	1	1	1	2			19 31.70
20 to 39				1		1	3	9	1	6	4	10	1	3	2	4	3	1	1	3	31 43.25
0 to 19																3	2			1	56 55.05
																				1	6 82.50
Total	2	10	10	14	8	4	8	18	4	9	8	11	4	4	3	8	6	3	1	1	139
Means of blood urea	160.0		77.1		58.2		46.8		42.2		36.4		42.1		28.2		32.2			26.0	

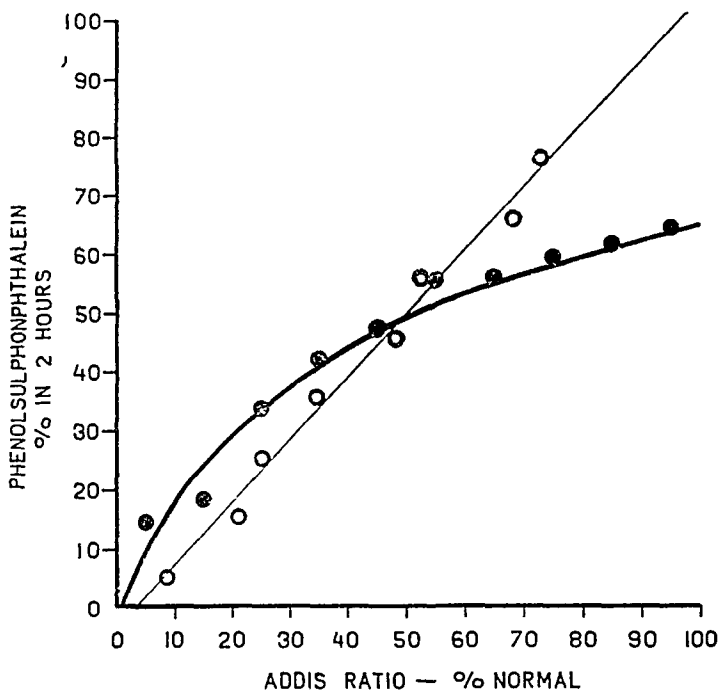


Chart 2—The heavy line shows the regression of the Addis ratio (per cent of normal) on phenolsulphonphthalein  $x = 0.941y + 4.10$ . The light line shows the regression of the phenolsulphonphthalein excretion on the Addis ratio  $y = 41.16 + 0.2315x - 42.93e^{-0.0478x}$ . In each case the Addis ratio is denoted by  $x$ , the other variable by  $y$ .

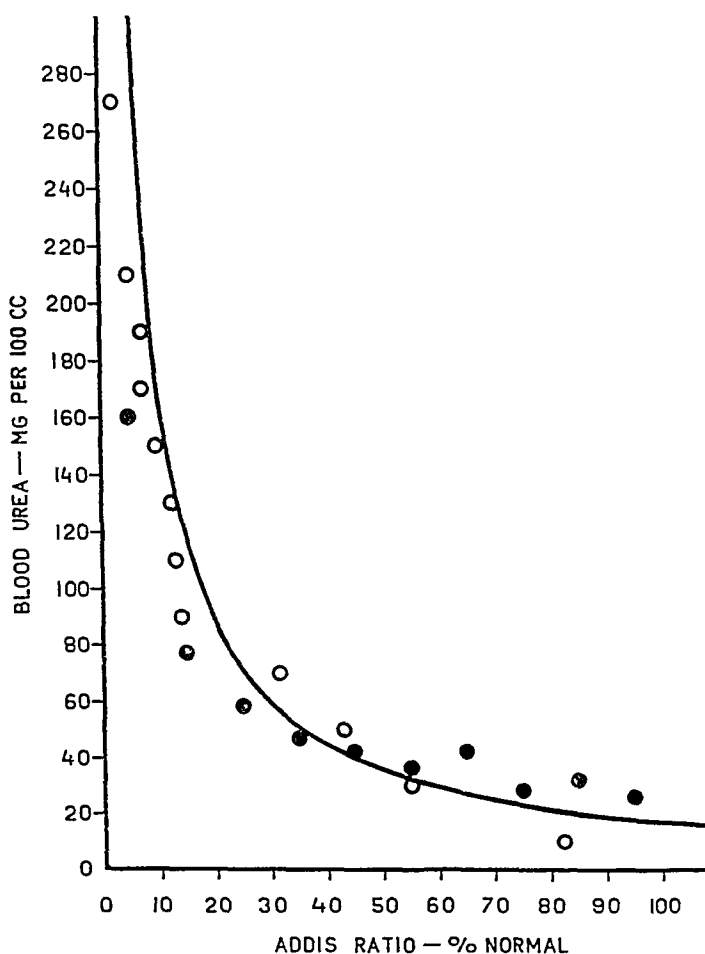


Chart 3—The solid dots represent the regression of blood urea on the ratio and the open dots, the regression of the ratio on the blood urea. The relationship of the Addis ratio (per cent of normal) and blood urea is  $xy = 1,755$ . The Addis ratio is denoted by  $x$ , the blood urea by  $y$ .

## COMMENT

In figure 2, the heavy line with solid dots represents the regression of the phenolsulphonphthalein excretion on the ratio. Physiologically and for comparison with other tests it is the most interesting. Practically, the light straight line, which represents the regression of the ratio on the phenolsulphonphthalein excretion and predicts the ratio from the phenolsulphonphthalein excretion is of more concern here. The equation is almost  $x = y$ , and for clinical purposes is close enough. It is convenient to know that, for example, if 40 per cent of the injected dye is excreted in two hours, the most likely ratio is 40 per cent.

In figure 3 have been plotted the regression of blood urea on the ratio (solid dots) and of the ratio on blood urea (light dots). They indicate similar regression lines. For reasons which will be considered in more detail elsewhere and which are inherent in the ratio formula,  $\frac{UV}{B} = \text{ratio}$ , the blood urea-ratio curve should be a rectangular hyperbola, equation  $xy = k$ , or the blood urea times the ratio equals a constant, the rate of excretion of urea. This constant is 1,755 in the present data, which fit the theoretical curve fairly well. Clinically, then, one divides 1,755 by the blood urea to get the per cent of the normal ratio.

Rytand<sup>17</sup> calculated the odds of prediction of the amount of functioning renal tissue from other variables. The same thing has been done here. The ratio is predicted from the blood urea excretion by dividing 1,755 by the observed urea concentration, and from the phenolsulphonphthalein excretion by the formula, percentage of phenolsulphonphthalein excretion equals ratio (instead of the more accurate mathematical regression of  $0.941y + 4.1$ ). The predictions in the one hundred and thirty-nine tests were compared with the actual ratios and the root-mean-square deviations of the errors calculated. The deviations were 16.71 for phenolsulphonphthalein and 19.10 for urea concentration. These results mean roughly that the odds are 2.15 to 1 in favor of a prediction being within  $\pm 17$  per cent of the true value when phenolsulphonphthalein is used, and within  $\pm 19$  per cent when the blood urea concentration is used to estimate the amount of functioning renal tissue (always in per cent of normal). The correlations are obviously better when the renal function is low. Separating the observations, the deviations are such that the odds are 2 to 1 in favor of the ratio predicted from the phenolsulphonphthalein excretion being  $\pm 19.5$  per cent of the true value when the observed excretion of phenolsulphonphthalein is 45 per cent of the injected amount or higher and  $\pm 13.5$  per cent when it is lower. Predicting from the blood urea concentration, the odds are 2 to 1 that the ratio will be  $\pm 15.4$  per cent of the true value when the observed blood urea concentration is 40 mg per hundred cubic centimeters or higher and  $\pm 22.9$  per cent when the observed blood urea concentration is lower than 40.



Of the two variables examined here the phenolsulphonphthalein test is by far the best measure of functioning renal tissue, not so much because it has a comparatively high correlation with the Addis ratio but because it happens to have a linear regression. On the basis of correlation with the ratio and the shape of the regression, a comparison of these variables with others which have been studied in the same manner<sup>17</sup> reveals that in order of value as measures of functioning renal tissue may be listed the "maximum rate of urine excretion," the excretion of phenolsulphonphthalein, the blood urea concentration and the specific gravity concentration. However, for practical purposes, because it is much easier for the physician and the patient and is most apt to be measured accurately, the phenolsulphonphthalein test may be considered the most valuable method of measuring function in the group.

The physiologic significance of the blood urea concentration-ratio regression in figure 3 will be considered elsewhere. The regression line of the excretion of phenolsulphonphthalein on the ratio in figure 2 falls smoothly along a parabola which may be extended to meet the origin. The excretion of phenolsulphonphthalein begins to decrease slightly when the amount of renal tissue becomes less than normal. When 50 per cent of the kidney has been removed the decrease in the excretion of phenol red becomes more and more rapid as the amount of renal tissue is reduced further.

#### SUMMARY

The significance of the phenolsulphonphthalein test of renal function and, secondarily, of the blood urea concentration was determined by a statistical analysis of the variables in relation to the Addis ratio as a measure of the amount of functioning renal tissue in a group of patients with Bright's disease.

Judged by their correlation and by the shape of their regression line with the ratio the phenolsulphonphthalein test is superior to the blood urea concentration as a measure of the amount of functioning renal tissue.

For certain clinical purposes the Addis ratio may be predicted as a per cent of normal from the blood urea by dividing 1,755 by the blood urea concentration and from the phenolsulphonphthalein test by multiplying the percentage of the dye excreted by 1.

The odds are 2 to 1 that the ratio may be predicted within a range of  $\pm 17$  per cent by means of the phenolsulphonphthalein test and of  $\pm 19$  per cent by means of the blood urea concentration.

Considering the individual observations, it is shown that both the blood urea concentration and the excretion of phenolsulphonphthalein may be well within normal limits until at least half the normally functioning renal tissue has been destroyed.

# Progress in Internal Medicine

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## ALLERGY

### A REVIEW OF CURRENT LITERATURE

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From January to June 1934, the *Quarterly Cumulative Index* lists under the heading "Anaphylaxis and Allergy" 206 titles. In 1933 there were 166 titles whereas five years before, in 1928, there were only 126 titles. Interest in the subject is growing rapidly in accordance with the discovery that the peculiar reaction of the host which is called "allergy" applies not only to hay fever, asthma and eczema but to a good many of the infectious diseases. The study of the host and the responses of the host to injuries and insults of wide variety is attracting the attention which it deserves. The subject is important. Even at this time, its scope is so large and the literature so voluminous that no review of this kind can possibly refer to each of the articles published. A great deal of selection has been necessary, and I hope that proper judgment has been exercised. No doubt, however, I have missed a number of important articles and thus failed to give credit to whom it is due. For this I am sorry. Incidentally, this review purports to deal with recent articles only.

### HISTORY OF ALLERGY

The history of bronchial asthma and allergy was recently summarized by Stolkind,<sup>1</sup> who laid stress on the antiquity of the disease. Asthma was recognized as a separate disease entity by the early Greeks, "who laid stress on changes in composition of the air, water and food as causes and mentioned the influence of nerves." "The next account of asthma of any importance was compiled by Moses Maimonides"—the Jewish physician to the Sultan, who lived in the twelfth century and four hundred years before such better known writers as van Helmont and Bonetus of the sixteenth and Thomas Willis of the seventeenth century.

### BROADENING CONCEPTION OF ALLERGY

Ever since the pioneer work of Walker, Goodale and Cooke twenty years ago, the word "allergy" has connoted the mechanism of hay fever, asthma and eczema—all three being diseases characterized by the urticarial type of reaction as demonstrated when the specific exciting cause

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1 Stolkind, E. The History of Bronchial Asthma and Allergy, *Proc Roy Soc Med* 26:36, 1933

is scratched or injected into the skin. More recently, other diseases which do not have the wheal and erythemic reaction have nevertheless been referred to as "allergic." Typical, of course, is the tuberculin reaction itself, a response which is delayed and which is inflammatory, but which depends nevertheless on a specific cause, like its immediate prototype. Syphilis and even typhoid fever have been placed in the category of delayed inflammatory skin reactions dependent on a change in the host brought about by the activity of the infectious agent. It was in 1928 that Swift and his associates<sup>2</sup> invoked allergy as a means of explaining the many different cultural findings by as many different students of arthritis, and others have fallen in with his idea. Thus Jenkins<sup>3</sup> and also Rackemann<sup>4</sup> reviewed the evidence for an allergic basis of rheumatism, while Jones and Mote<sup>5</sup> in an important piece of work demonstrated a relation between the immediate and the delayed reaction to streptococci in their rheumatic patients. This will be discussed later in more detail.

Meantime, the factor of change in the host as conceived in the word "allergy" has been utilized in the diagnosis of an increasing number of infectious diseases. New diagnostic methods based on allergy have been applied to a number of infectious diseases. In some of them, the intracutaneous injection of a specific antigen produces a skin reaction of the immediate urticarial type.

*Trichinosis*—Augustine and Theiler,<sup>6</sup> in a very complete study, described the development of an inflammatory edema which appears within an hour after the test and may be demonstrated in man as well as in animals some time—at least nine days—after infection. It is elicited by the intradermal injection of an extract of larvae, obtained most easily by peptic digestion of infected muscle. The reaction is sometimes, though not always, accompanied by the finding of precipitins in the circulating blood.

*Hookworm Disease*—Vattuone<sup>7</sup> discovered that an antigen prepared from ancylostomas will produce, within from fifteen to thirty minutes after intradermal injection, a clear whitish blister surrounded by a hyperemic circle about 2 cm. in diameter.

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<sup>2</sup> Swift, H. F., Derick, and Hitchcock. Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, *Tr. A. Am. Physicians* **43** 192, 1928.

<sup>3</sup> Jenkins, C. E. Anaphylactic Basis of Rheumatism, *Brit. M. J.* **1** 186, 1934.

<sup>4</sup> Rackemann, F. M. The Role of Allergy in Arthritis, *New England J. Med.* **208** 1347, 1933.

<sup>5</sup> Jones, T. Duckett, and Mote, John R. The Phases of Foreign Protein Sensitization in Human Beings, *New England J. Med.* **210** 120, 1934.

<sup>6</sup> Augustine, D. L., and Theiler, Hans. Precipitins and Skin Tests as Aids in Diagnosing Trichinosis, *Parasitology* **24** 60, 1932.

<sup>7</sup> Vattuone, A. B. New Intradermal Reaction in Ancylostomiasis, *M. J. Australia* **1** 645, 1933.

*Echinococcus Disease*—The Casoni reaction—an immediate urticarial response to the intradermal injection of cyst fluid—should be mentioned because, as previously described by Rackemann and Stevens,<sup>8</sup> it corresponds so closely to the familiar skin reactions to pollens and danders as used in cases of hay fever. Meantime, the purified carbohydrates of the pneumococci also have been shown to produce skin reactions of the immediate urticarial type, which Francis<sup>9</sup> found to have some therapeutic and prognostic importance. Meantime, too, Boor and Miller<sup>10</sup> have been working with carbohydrates purified from the bacterial substance of the gonococcus and of the meningococcus.

The reactions described are all to be classified as immediate responses of the urticarial type. Other newly described reactions are delayed and inflammatory, like the tuberculin reaction.

*Undulant Fever*—Undulant fever due to infection with *Brucella abortus* (Bang) and with the *melitensis* group of organisms, including the *brucella* organisms, has been extensively studied by means of skin tests since the new method was described by Burnet<sup>11</sup> in 1922. Burnet used a broth filtrate which he called "melitin." Goldstein<sup>12</sup> reviewed the literature following Burnet's article and described the inflammatory reaction which develops at the site of intradermal injection of a vaccine containing 500,000,000 abortus organisms to the cubic centimeter. He states that a fat-free antigen is preferable, because the vaccine may induce severe local and general reactions. According to Goldstein's tables, the skin test bears no relation to preexisting agglutinins. It is frequently positive when agglutinins are absent. After the skin tests have been made, however, agglutinins rise rapidly in most of the cases. Injection by the intradermal route gives rise to antibodies, as will be discussed later. *Brucella* vaccine has also been used in cattle to diagnose contagious abortion, the result of the test being entirely comparable with the result of the test with tuberculin.

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8 Rackemann, F. M., and Stevens, A. H. Skin Tests to Extracts of *Echinococcus* and *Ascaris*, *J. Immunol.* **13** 389, 1927.

9 Francis, Thomas, Jr. The Value of the Skin Test with Type-Specific Capsular Polysaccharide in the Serum Treatment of Type I *Pneumococcus* Pneumonia, *J. Exper. Med.* **57** 617, 1933.

10 Boor, A. K., and Miller, C. Philip. A Study on Bacterial Proteins with Special Consideration of *Gonococcus* and *Meningococcus*, *J. Exper. Med.* **59** 63, 1934.

11 Burnet, E. Sur un nouveau procédé de diagnostic de la fièvre méditerranéenne, *Compt. rend. Soc. de biol.* **174** 421, 1922.

12 Goldstein, Jacob D. Cutaneous Reactions in the Diagnosis of Undulant Fever, *J. Clin. Investigation* **13** 209, 1934.

*Lymphogranuloma Inguinale*—The Frei reaction,<sup>13</sup> described in 1925, is another excellent example of allergy. Cole<sup>14</sup> described the method of making the antigen—essentially an emulsion of infected lymph nodes—and the inflammatory reaction which follows its intradermal injection. His article has a number of striking photographs.

*Skin Diseases*—It is, however, in the realm of skin diseases that the broader conception of allergy has developed into practical importance. Another variation in the type of allergic reactions was recognized in 1929 by Bloch<sup>15</sup> when he became interested in his patch tests. Shortly after that, Williams<sup>16</sup> of New York made an important contribution when he discussed the difference between the direct effect of parasites on the skin, which he called “dermatoses,” and the indirect effect, which he called “dermatids” and which he interpreted as allergic. This subject will be referred to later.

#### RELATION BETWEEN VARIOUS PHASES OF ALLERGY

The relation between the various phases of allergy has been recently studied and with great interest and profit. In 1928, Dienes<sup>17</sup> found that when guinea-pigs were treated with intradermal injections of foreign serum or of egg-white, given daily, the responses, if carefully observed, were found to consist at first of a definite red inflammatory reaction appearing within about twenty-four hours after the injection. This delayed reaction appeared within three or four days after the beginning of treatment. Later, however, when the daily injections were continued for eight or ten days, the responses became of the immediate urticarial type and then were found to be accompanied by the development of circulating antibodies in the guinea-pig. In the spring of 1933, Jones and Mote<sup>5</sup> made similar observations on children who for another purpose were given repeated intradermal doses of rabbit peritoneal fluid. Within a few days a reaction of the delayed inflammatory type appeared in these children. Later, however, after about ten days, the intradermal doses were found to produce a reaction of the immediate urticarial type. At about the same time, Simon and Rackemann<sup>18</sup> dis-

13 Frei, Wilhelm. Eine neue Hautreaktion bei “Lymphogranuloma Inguinale,” *Klin Wchnschr* **4** 2148, 1925.

14 Cole, H. N. Lymphogranuloma Inguinale, Fourth Venereal Disease. Its Relation to Stricture of the Rectum, *J A M A* **101** 1069 (Sept 30) 1933.

15 Bloch, Bruno. The Rôle of Idiosyncrasy and Allergy in Dermatology, *Arch Dermat & Syph* **19** 175 (Feb) 1929.

16 Williams, C. M. Enlarging Conception of Dermatophytosis, *Arch Dermat & Syph* **15** 451 (April) 1927.

17 Dienes, Louis. Further Observations Concerning the Sensitization of Tuberculous Guinea Pigs, *J Immunol* **15** 153, 1928.

18 Simon, F. A., and Rackemann, F. M. The Development of Hypersensitiveness in Man. I. Following Intradermal Injection of the Antigen, *J Allergy* **5** 439, 1934.

covered that repeated doses of guinea-pig serum given intradermally either to so-called allergic patients or to so-called normal persons resulted in the development first of the delayed and later of the immediate type of reaction, the latter being associated with antibodies which could transfer the local skin reaction to the arm of a normal person. It should be noted that this reaction was quite the same in the allergic patients as in the normal controls. As Jones and Mote pointed out, it is evident that these two reactions represent different phases of the response which the normal animal or man exhibits toward repeated intradermal doses.

In a recent article, I<sup>19</sup> yielded to the temptation of suggesting that arthritis and certain other chronic infectious processes represent the early stage of the process of immunity, that hay fever, asthma and eczema represent a later stage (the two diseases are rarely combined in the same patient—which is interesting because both are so common in the community), and that patients continue to have these diseases because they are unable to escape into the final stage called “immunity.” They become “stuck” in one or other allergic phase.

*Sensitiveness Can Be Artificially Produced in Man*—The experiments of Jones and Mote and of Simon and Rackemann just mentioned have been amplified. Simon<sup>20</sup> has been able to sensitize the nasal mucous membrane so that a second application of a pledget wet with guinea-pig serum and placed in the nose from seven to fourteen days after the first results in a violent attack of symptoms resembling those of hay fever.

These reactions are typical enough, but they are transitory. Further study, as yet incomplete, shows that sensitiveness artificially produced in normal persons tends slowly to disappear, it is not permanent and there is, therefore, grave question whether the behavior of an allergic person does not depend on something more fundamental than a mere quantitative change. The whole question of the influence of heredity in allergy is still pertinent. Not yet can one explain why it is that some people rather than others seem to have the capacity to develop hypersensitiveness and the *Reaktionfähigkeit* which von Pirquet<sup>21</sup> described. The distinction between sensitization and anaphylaxis remains one of the problems in man. Although it is easy to produce sensitiveness of the skin with appearance of reagins in the blood, no clinical picture analogous to that of natural hay fever or asthma has so far been observed. The observations of Simon concern a temporary change only.

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19 Rackemann, F. M. A Review of the Phases of Allergy, *J. Allergy* **6** 7, 1934.

20 Simon, F. A. The Development of Hypersensitiveness in Man. II. Absorption of the Antigen Through the Nasal Mucous Membrane, *J. Allergy* **5** 451, 1934.

21 von Pirquet, C. Allergie, *München med. Wchnschr.* **53** 1457, 1906.

## THE HOST FACTOR IN ALLERGY

The host factor in allergy has been studied to some extent. The differences between allergic patients and normal persons have been investigated from the point of view of physiology and of immunology.

*Physiologic Observations*—The physiologic studies are interesting, although it is hard to know whether they indicate results of an allergic process or its cause. Kern and Teller<sup>22</sup> studied the basal metabolism in asthma and eczema, finding frequently a subnormal rate. They felt, however, that their results were an effect and not a cause of the allergic state. At the same time, they estimated the total blood calcium in 75 patients and found it within normal limits in practically all of them. Lierle and Sage<sup>23</sup> reopened the question of the calcium, phosphorus and potassium content of the serum and spinal fluid in asthma. They carefully reviewed the findings of many others, comparing them with their own, and concluded that data on the calcium, phosphorus and potassium of the serum and spinal fluid showed no striking departure from normal values. This paper is important because of the suggestion made originally by Cantarow<sup>24</sup> that the calcium in the spinal fluid is analogous to the diffusible calcium in the blood. Black<sup>25</sup> studied the blood sugar in allergic persons, finding it low, but here again the low level might well have been a cause rather than an effect of the allergic response. One is reminded of Beckman's<sup>26</sup> theory that allergy is a special type of alkalosis amenable to treatment with large doses of acid. On the whole, it is clear that so far, at least, physiologic studies fail to reveal a difference between allergic and normal persons.

*Immunologic Observations*—The immunologic studies are more important. In 1930, Cohen, Ecker, Breitbart and Rudolph<sup>27</sup> studied the rate of absorption of ragweed pollen blown into the nose. A site in the skin was sensitized passively by an intradermal injection of serum from a ragweed-sensitive patient, and twenty-four hours later ragweed pollen was blown into both nostrils. Within a few minutes an urticarial

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22 Kern, R. A., and Teller, Ida. Basal Metabolism and Blood Calcium Studies in Asthma and Allergic Eczema, *J. Allergy* **2** 488, 1931.

23 Lierle, D. M., and Sage, R. A. A Study of the Calcium, Phosphorus and Potassium of the Serum and Spinal Fluid in Asthma, *J. Allergy* **3** 325, 1932.

24 Cantarow, A. Calcium Studies. V. The Relationship Between the Calcium Content of Cerebrospinal Fluid and Blood Serum, *Arch. Int. Med.* **44** 667 (Nov.) 1929.

25 Black, J. H. Blood Sugar in Allergic Persons, *J. Texas State Med.* **29** 257, 1933.

26 Beckman, Harry. Allergy Considered as a Special Type of Alkalosis, *J. Allergy* **1** 496, 1930.

27 Cohen, M. B., Ecker, E. E., Breitbart, J. R., and Rudolph, J. A. The Rate of Absorption of Ragweed Pollen Material from the Nose, *J. Immunol.* **18** 419, 1930.

wheel appeared at the site of cutaneous sensitization. A comparison of the time of appearance of the wheel in minutes in allergic patients with the time in normal persons showed that the wheel appeared much faster in the nonatopic persons than in the allergic patients. These findings agree closely with those of Brunner and Walzer,<sup>28</sup> who in 1928 found that the response in the sites of passive sensitization of the skin after the ingestion of raw fish was faster in normal persons than in allergic patients. Here attention should be called to the excellent review of the literature on the passage of native proteins through the normal gastro-enteric wall by Ratner and Gruehl.<sup>29</sup> In 1933, Cohen and Rudolph<sup>30</sup> extended their studies and confirmed them in a larger series of patients. In the same article, they described their experiences with histamine, stating that the wheals due to histamine, when excised from the skin and examined microscopically, show smaller reactions in normal, nonatopic persons than in atopic patients. McConnell,<sup>31</sup> working in Alexander's clinic, measured very accurately the size of the wheal produced by the intradermal injection of precise doses of a 1:2,000 dilution of histamine, and found that in allergic persons, between attacks, the wheals are smaller, but that during attacks they remain of the same size as in normal persons, and incidentally that this normal size varies considerably from 1.2 to 1.7 sq cm. Rackemann, Simon and Scully<sup>32</sup> made a similar study, but in place of measuring the wheal obtained with any one dilution, they studied the reaction of their patients and controls to serial dilutions of histamine and found that the differences between normal persons and allergic patients in their response to skin tests with dilutions of histamine were negligible.

The response to typhoid vaccine was studied in the same article, and it was shown that the development of typhoid agglutinins following treatment with typhoid vaccine was essentially the same in a group of 20 patients with asthma as it was in another group of 23 normal nurses in the hospital training school. So far, then, it is not possible to show any particular difference between the immunologic responses of asthmatic patients and normal persons.

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28 Brunner, M., and Walzer, M. Absorption of Undigested Proteins in Human Beings, Absorption of Unaltered Fish Proteins in Adults, *Arch Int Med* **42** 172 (Aug.) 1928.

29 Ratner, Bret, and Gruehl, H. L. Passage of Native Proteins Through the Normal Gastro-Enteric Wall, *J Clin Investigation* **13** 517, 1934.

30 Cohen, M. B., and Rudolph, J. A. Atopic and Bacterial Asthmatic Patients. Some Immunologic and Histologic Evidences of a Fundamental Difference Between Them, *J Allergy* **4** 367, 1933.

31 McConnell, F. S. Observations on the Formation of Wheals. VI Response of Normal and Allergic Individuals, *J Allergy* **4** 177, 1933.

32 Rackemann, F. M., Simon, F. A., and Scully, M. A. Further Observations on the Nature of Allergy, *J Allergy* **4** 498, 1933.



In the meantime, it is pertinent to recall the work of Woringer,<sup>33</sup> who studied a group of 71 eczematous infants and divided them into two groups. One group he called *holoallergique* because they had antibodies in their blood and also reacted with an urticarial wheal on being tested with egg-white. Some of them also presented urticaria and asthma when egg-white was injected subcutaneously. The other group he called *dermoallergique* because no antibodies could be demonstrated and the sensitiveness was evidently limited to the skin.

Related work is that by Pilcher,<sup>34</sup> who made skin tests on the hairless area over the back of the guinea-pig's neck, using histamine in normal guinea-pigs and horse serum in sensitive animals. The responses in the two experiments were about the same, although the horse serum wheal had a more gradual and chronic development. Its size bore a definite relation to the degree of anaphylactic sensitiveness. The histamine wheal, however, remained the same in the normal and sensitized groups.

Studies of the host factor from a different point of view were started by Goodner,<sup>35</sup> who tried to find out why specific antipneumococcic serum was more active in certain rabbits than in others. The conclusions drawn from an elaborate and interesting series of experiments is that animals which are heavy and have high leukocyte counts are not only more resistant to the infection but are better able to utilize the immune principles passively conferred by immune serum.

#### CHEMISTRY OF HYPERSENSITIVENESS

The chemistry of hypersensitiveness has received further attention. Landsteiner and van der Scheer,<sup>36</sup> in 1933, prepared new antigens from horse serum and azodyes such that animals prepared with these materials would undergo fatal shock when tested intravenously with solutions of the dyes alone. The chemistry of serum sickness was studied by Jones and Fleisher,<sup>37</sup> who found that the pseudoglobulin was the principle in horse serum most active in causing symptoms. Swineford<sup>38</sup> also found that the globulin fraction was most active. When solutions

33 Woringer, Pierre. L'allergie au blanc d'oeuf chez le nourrisson, *Presse med* **40** 1383, 1932.

34 Pilcher, Lewis S. The Urticarial Skin Reaction in Normal and Sensitized Guinea Pigs, *J Immunol* **25** 11, 1933.

35 Goodner, Kenneth. Studies in Host Factors in Pneumococcus Infections. I. Certain Factors Involved in the Curative Action of Specific Antipneumococcus Serum in Type I Pneumococcus Dermal Infection in Rabbits, II. The Protective Action of Type I Antipneumococcus Serum in Rabbits, *J Exper Med* **60** 9, 1934.

36 Landsteiner, K., and van der Scheer, J. Anaphylactic Shock by Azodyes, *J Exper Med* **57** 633, 1933.

37 Jones, L. R., and Fleisher, M. S. Relation of Serum Reaction to Serum Sickness in Rabbits, *Proc Soc Exper Biol & Med* **30** 1195, 1933.

38 Swineford, Oscar. Studies of Anaphylactic Antibody, *J Allergy* **5** 265, 1934.

of the globulin in rabbit antihorse serum were treated with increasing quantities of sodium sulphate, the antibody was precipitated quantitatively according to the concentration of the salt. The point of his paper, however, is that the concentrated antibody solution thus obtained was able to protect sensitized guinea-pigs from horse serum shock. The variety of newly identified materials capable of inducing allergy in sensitive persons will be reviewed later in an appendix.

#### IMMUNOLOGY OF HYPERSENSITIVENESS

*Origin of Sensitiveness*—Moll<sup>39</sup> presented new evidence of true occupational asthma, which means in turn that hypersensitiveness may be acquired by the inhalation of foreign dusts. Among a considerable group of patients with occupational asthma, he found 19, or 47 per cent, who were sensitive to sheep wool. This sensitiveness occurred in weavers and menders as well as in workers in a clothing warehouse. Three farmers were sensitive to pollen. Two bakers were sensitive to wheat. Eight handlers of animals and their fur reacted to animal danders. A joiner was sensitive to glue. Two dyers, a seamstress and a surgical nurse were sensitive to the dust of cotton, and three shop assistants were sensitive to house dust. This is further evidence that hypersensitiveness may be acquired. Sensitization by feeding is an important subject which was very carefully reviewed by Ratner and Guehl<sup>40</sup> in an excellent article giving 86 references. Evidently, it is quite possible to show that native protein can pass unchanged through the normal gastro-enteric wall both in animals and in man. Ross<sup>40</sup> produced immunity in rats by feeding killed cultures of *Pneumococcus*, type I, by mouth.

*Parts Played by Different Tissues*—Different tissues play different parts in the development of hypersensitiveness. It was Bloch<sup>41</sup> who first pointed out that in contact eczema the sensitiveness is of the skin alone and not of any other tissue. Naegeli and his co-workers<sup>41</sup> observed that in cases of drug allergy, notably sensitiveness to antipyrine, certain local areas of the skin became sensitive, and that when the skin over these areas was transplanted to other, normal sites it carried the sensitiveness with it. Wise and Sulzberger<sup>42</sup> likewise worked with surgical skin transplants, but their results were different. When sensitive and normal skin were interchanged and the transplants were allowed to heal,

39 Moll, H. H. Occupational Asthma with Reference to Wool Sensitivity, *Lancet* **1** 1340, 1933.

40 Ross, Victor. Immunity in Rats Produced by Feeding the *Pneumococcus* Type I, *J. Immunol.* **27** 235, 1934.

41 Naegeli, O., de Quervain, F., and Stalder, W. Nachweis des cellularen Sitzes der Allergie beim fixen Antipyrinexanthem, *Klin. Wchnschr.* **9** 924, 1930.

42 Wise, Fred, and Sulzberger, M. B. Drug Eruptions. I. Fixed Phenolphthalein Reactions, *Arch. Dermat. & Syph.* **27** 549 (April) 1933.

the reaction remained in the old sensitive area when the patient took the offending drug, it did not follow the sensitive skin itself

More recently, Dienes<sup>43</sup> pointed out that the necrotic reactions of the skin are not simply the expression of a high degree of sensitiveness, because they are quite independent of any general sensitiveness, and furthermore, microscopic study shows that the necrosis is limited to the skin itself. Further evidence on the function of the skin was presented by Simon and Rackemann<sup>44</sup> in their work on poison ivy when they showed that guinea-pigs could be made skin-sensitive to *Rhus toxicodendron* but only when the extract was applied to the skin surface itself, no result followed subcutaneous, intraperitoneal or intravenous injection of poison ivy extract. Meantime, as noted previously, Scon<sup>18</sup> was able to sensitize the skin of guinea-pigs, rabbits and man to various foreign proteins by repeated intradermal injections, producing results with fair regularity. In contrast to this, however, Brunner<sup>45</sup> had no success when, in an analogous experiment, his doses of rabbit epithelium and egg-white were given subcutaneously instead of intradermally. Sensitiveness (as determined by positive skin tests) did not develop in his animals. The last observation is very interesting because it confirms the fact that the skin itself is an organ which has important immunologic functions.

The observations of Stevens<sup>46</sup> are somewhat in line. He made a comparison of pulmonary and dermal sensitivity to inhaled substances, and found that among 45 patients with asthma 11 failed to give a skin reaction to any of 90 different substances, and that these 11 patients also failed to react when tested by inhaling sprays of the specific substances. Thirty-four patients were skin-sensitive. However, of these, only 15 or less than half reacted to inhalant tests, and 9 of the 15 reacted to only one inhalant test. In 39 instances, the skin reaction was strongly positive and yet an attack of asthma resulted from the inhalation of the corresponding extract in only seven instances—a ratio of 1/5. With 53 moderate skin reactions and 76 weak skin reactions, the inhalation test was positive in only 6 and 2 instances, respectively. On the other hand, the skin test was quite negative in 410 instances, and yet asthma followed the inhalation test in 10.

Stevens' study demonstrates that in asthma a marked discrepancy exists between skin tests and inhalant tests. His work is important, for it gives strong support to the clinical observation of a marked dis-

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43 Dienes, Louis. The Participation of Cutaneous Epithelium in Immunity Response, *J. Immunol.* **24** 253, 1933.

44 Simon, F., Simon, M. G., Rackemann, F. M., and Dienes, Louis. The Sensitization of Guinea Pigs to Poison Ivy, *J. Immunol.* **27** 113, 1934.

45 Brunner, Matthew. Active Sensitization in Human Beings, *J. Allergy* **5** 257, 1934.

46 Stevens, Franklin A. A Comparison of Pulmonary and Dermal Sensitivity to Inhaled Substances, *J. Allergy* **5** 285, 1934.

crepancy between positive skin tests and the precise causes of symptoms. It will be referred to again.

No review of tissue sensitiveness can be complete without reference to the extensive and complete studies of Kahn.<sup>47</sup> Having established the method of injecting equal quantities of serial dilutions of a protein like egg-white into the layers of the skin of sensitized rabbits and using the local reactions which develop in a few hours as a measure of sensitiveness, Kahn found that in the case of egg-white the titers of skin sensitivity and serum precipitin are somewhat parallel, but that after a time (from thirty to sixty days) the precipitins fall off while the skin sensitivity remains. Intermediate tests for this sensitivity have perhaps served to maintain it. When the sensitive rabbit is then given an intravenous injection of the protein, desensitization occurs at once, the serum precipitins and the cutaneous sensitivity both fall abruptly. However, the low level is maintained for only a short time (from twenty-four to forty-eight hours), and soon both phenomena reappear, usually in higher titer than before—the precipitins attaining a level somewhat higher than that of the skin sensitivity.

When the same methods are applied to experiments with bacteria (study X), the results are much the same. Repeated intracutaneous injections result in a rapid development of skin reactivity to the suspension of killed organisms used. Serum agglutinins develop, but their titer is low. When, however, the vaccine is given intravenously, the serum agglutinins reach a high point while the skin sensitivity is low. The route of administration is all-important, and the choice of organism used in the experiment makes little difference.

In the bacteria-treated animals, however, desensitization by large doses of killed organisms given intravenously has effects different from those in the protein-treated animals. The skin reaction almost disappears in both groups, but whereas the protein precipitins fall, the serum agglutinins for bacteria maintain their level. Kahn wisely noted that in testing for precipitins the amount of serum used is large while that of protein is small, whereas in testing for agglutinins the amount of serum is small while that of bacteria is large. Perhaps precipitins are absorbed from the circulation more rapidly than agglutinins. However, the desensitized state is brief, and now comes an interesting observation. A few hours after the intravenous dose, the sites of former tests become inflamed, red, purple and finally black with definite necrosis. Still later, the skin sensitivity returns.

From this observation Kahn has drawn an interesting comparison with the chance of syphilis. According to his theory, the spirochetes invade without resistance until they reach the blood stream. Meantime, the

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<sup>47</sup> Kahn, Reuben L. Studies in Tissue Reactions in Immunity, *J. Immunol.* 25: 295, 1933.

skin has been sensitized, and now the development of circulating antigen results in a sudden desensitization of the skin which is followed quickly by a necrotic reaction. In study XIII, Kahn showed that in rabbits naturally sensitive to certain organisms desensitization by intravenous treatment results in a transient disappearance of skin sensitivity quite as in the sensitized animals. Furthermore, in a short time the sites of tests made before desensitization show a slow development of inflammation which goes on to necrosis as in the treated group of animals.

In the same field is the work of Rich, Jennings and Downing,<sup>48</sup> who inquired "Is immunity achieved through allergy?" Choosing an organism particularly virulent for rabbits (*Pasteurella aviseptica*), they produced immunity by giving the vaccine subcutaneously, and then observed the development of large local reactions to their treatment. The animals became sensitized, and some of them were then given large doses of killed bacteria intravenously. Severe symptoms resulted but passed off in most instances. Then the desensitized group of rabbits, the immunized group and a third control group were all given doses of the living organisms intracutaneously. The desensitized animals showed no local reactions up to twenty-four hours. The immune animals displayed a large angry inflammation which in twenty-four hours became necrotic and later discharged pus, with prompt recovery. The controls also showed a large local reaction, but it developed a little more slowly at first, becoming extensive later, with a hemorrhagic ulceration before death, which occurred in less than forty-eight hours. Experiments with pneumococci gave entirely similar results, and incidentally desensitization could be effected by nonspecific means, since animals vaccinated with *Past. aviseptica* could be desensitized by suspensions of killed pneumococci and vice versa. The point of their experiment was that in the desensitized animals a high immunity could persist in the absence of skin sensitivity and without the development of local inflammation.

This dissociation of allergy and immunity, demonstrated so clearly, is shown also by Kahn's work in which the lack of correlation between the titers of circulating antibody and skin sensitivity is frequently noted. Perhaps one must think of the skin and its sensitiveness as presenting a phenomenon different from anaphylaxis and immunity, but in doing so one must admit that the relation is a close one.

*The Eye Can Be Sensitized*—The two Seegals with Khorazo<sup>49</sup> found that when egg-white is injected into the anterior chamber of the rabbit's

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48 Rich, A. R., Jennings, F. B., and Downing, W. M. Persistence of Immunity After Abolition of Allergy by Desensitization, *Bull. Johns Hopkins Hosp.* **53** 172, 1933.

49 Seegal, Beatrice C., Seegal, David, and Khorazo, D. Local Organ Hypersensitiveness. V. The Fate of Antigen and the Appearance of Antibodies During the Development of Hypersensitiveness in the Rabbit Eye, *J. Immunol.* **25** 207, 1933.

eye, the eye is sensitized so that later an intravenous dose of the specific substance (egg-white) causes an acute inflammation in it. In another study, the Seegals<sup>50</sup> observed that repeated injections of this protein into the eye result in the development of precipitins, and that when this occurs the egg-white is found to have disappeared from the eye. Irritation of the eye by glycerin followed by intravenous injection of egg-white results in a specific local sensitiveness of the eye. The antigen becomes fixed to the injured tissue so that when, later on, another intravenous dose is given, a specific reaction follows. These experiments remind one of the relation of any infectious process to sensitization. Dienes<sup>51</sup> was the first to show that when egg-white is injected directly into a tuberculous lesion the character and the degree of the resulting sensitiveness are quite different from what they are when the same material is injected into a normal area.

While tissue reactions are of great immunologic importance in the host factor, the behavior of the animal to serums of different kinds is an important item.

*Normal vs Immune Serum*—In 1929, Tuft and Ramsdell<sup>52</sup> observed that whereas normal horse serum is weakly antigenic in the rabbit, immune horse serum is highly antigenic, producing precipitins, positive skin reactions and an anaphylactic antibody in high concentration. In spite of this, however, they found that serum disease as demonstrated by the use of dyes occurred with equal frequency whether normal or immune serum was used. In a recent article, Tuft<sup>53</sup> investigated the question of whether the antibody response might not depend simply on the concentration of the immune serum. By precipitation with ammonium sulphate, he obtained a concentrate 1 cc of which was equivalent to 12.5 cc of normal horse serum. The increase in antibodies which followed its use was, however, small. These findings were confirmed by L. R. Jones<sup>54</sup>.

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50 Seegal, Beatrice C., and Seegal, David. Local Organ Hypersensitiveness. VI. An Indirect Method for Its Production in the Rabbit Eye, *J Immunol* **25** 221, 1933.

51 Dienes, Louis. The Immunological Significance of the Tuberculous Tissue, *J Immunol* **15** 141, 1928; Factors Conditioning the Development of the Tuberculin Type of Hypersensitivity, *ibid* **23** 11, 1932.

52 Tuft, Louis, and Ramsdell, Susan G. The Antibody Response in the Human Being After Injection with Normal Horse Serum, *J Exper Med* **50** 431, 1929.

53 Tuft, Louis. Further Studies in Serum Sickness. IV. Effect of Concentration of Normal Horse Serum upon Antibody Response, *J Immunol* **24** 25, 1933.

54 Jones, L. R. Skin Sensitivity and Antibody Production upon Administration of Normal and Immune Serum in Rabbits, *Proc Soc Exper Biol & Med* **31** 190, 1933.

*Heterologous Serum*—As used in the transfer of anaphylaxis and of immunity, heterologous serum gives rise to a similar problem. Khorazo<sup>55</sup> pointed out that horse serum is more likely than other kinds to produce serum disease in rabbits. Mehlman and Seegal<sup>56</sup> agreed with Avery and Tillett<sup>57</sup> that antipneumococcic serum from the rabbit will passively sensitize a guinea-pig whereas antipneumococcic serum from the horse will not do so. In dogs, however, the horse immune serum will transfer the sensitiveness to the pneumococcic carbohydrate without difficulty. Evidently there is some unknown peculiarity in the two hosts—the guinea-pig and the dog.

Somewhat analogous are the rather complicated observations of Burky<sup>58</sup>. Knowing that an extract of the lens of the eye will react on cataractous persons but not on normal persons, he attempted to sensitize the rabbit to lens protein. Chopped beef lens was incubated in hormone broth, and then the mixture was inoculated with *Staphylococcus aureus* and allowed to stand for ten days. Rabbits given injections of the filtrate became sensitive so that they would react to the simple lens extract. They were made sensitive to a part of their own tissue. Similarly, rabbits treated with rabbit muscle hormone broth were made sensitive to an extract of rabbit muscle, and the reactions were specific in that the muscle-treated animals would not react to lens any more than the lens-treated animals would react to muscle. Ragweed was used, and Burky observed that ragweed broth toxin also was capable of sensitizing rabbits, causing them to produce precipitins and so changing the animals that they would react later with asthma when placed in an atmosphere of pollen dust. It is important to recognize that Burky's sensitizing doses were given intracutaneously with good results just as Simon and Rackemann had good results in sensitizing man and animals when the doses were given intracutaneously.

#### DESENSITIZATION

A pertinent editorial<sup>59</sup> in *The Journal of the American Medical Association* for March 3, 1934, quotes Wells in reviewing the four

55 Khorazo, D. So-Called "Serum Sickness" in Rabbits Following the Intravenous Injection of Various Foreign Serums, *J Immunol* **25** 113, 1933.

56 Mehlman, Julia, and Seegal, Beatrice C. Passive Sensitization of the Guinea Pig with Rabbit and Horse Antipneumococcus Type I Serum, *J Immunol* **26** 1, 1934, A Comparison of the Sensitizing and the Therapeutic Effect of Rabbit and Horse Antipneumococcus Type I Serum in Albino Mice, *ibid* **27** 81, 1934.

57 Avery, O. T., and Tillett, W. S. Anaphylaxis with the Type-Specific Carbohydrate of Pneumococcus, *J Exper Med* **49** 251, 1929.

58 Burky, E. L. The Production in the Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extracts by the Action of *Staphylococcus* Toxin, *J Allergy* **5** 466, 1934.

59 Allergy in Animals, Editorial *J A M A* **102** 694 (March 3) 1934.

ways in which animals become refractory 1 Desensitization is the exhaustion of antibodies 2 Antianaphylaxis is a condition of circulating antibodies in excess 3 Antisensitization is a condition in which the blood has antibodies against the sensitizing serum 4 Tissue inactivation is a condition in which, through exhaustion or drug action, the sensitized cells cannot respond

With this summary in mind, the next four papers are of interest Duthoit<sup>60</sup> threw further light on the advantages of treatment by the intradermal route Thinking that many intradermal doses are in fact subcutaneous, he dissected a layer of the skin so that he could lift a flap free from the body and in this way demonstrate that his injection could not enter the subcutaneous tissue By this method, 6 of 16 sensitive animals were successfully protected against anaphylactic shock Although he<sup>61</sup> showed in the following paper that the duration of the protection was only five days, evidently the exhaustion of antibodies can be accomplished by the intradermal route

The effect of reticulo-endothelial blockade on the formation of antibodies in rabbits was studied by Tuft,<sup>62</sup> who showed that after injection of an 8 per cent suspension of india ink, whether given intravenously or intraperitoneally, the development of immunity is prevented and the titer of agglutinins, if these are already present, tends to fall Somewhat similar in effect were the experiments of Hanger,<sup>63</sup> who found that the addition of egg lecithin to fatal doses of serum prevented a fatality in sensitive rabbits Hanger disclosed that the nature of the protection is unknown, but his work and Tuft's work suggest a fifth mechanism for desensitization, namely, a mechanical blockade of the sources of antibodies

Meantime, Beckman<sup>64</sup> collected the results of his treatment of patients with hay fever by large doses of acid given by mouth, he reported successful results in 69 per cent of the patients treated by this method as compared with 70 per cent of over 2,000 patients treated by desensitization as reported in the literature Here is a direct effect on the host factor, but its nature is unknown

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60 Duthoit, A A propos de l'antianaphylaxie par voie intradermique, *Compt rend Soc de biol* **112** 384, 1933

61 Duthoit, A Sur la durée de la vaccination antianaphylactique, *Compt rend Soc de biol* **112** 385, 1933

62 Tuft, Louis The Effect of Reticulo-Endothelial Cell Blockade upon Antibody Formation in Rabbits, *J Immunol* **27** 63, 1934

63 Hanger, Franklin M The Influence of Lipoids in Tissue Immune Reactions, *abstr, J Clin Investigation* **13** 692 (July) 1934

64 Beckman, H Treatment of Hay Fever by Desensitization and with Acid, *Lancet* **1** 1227, 1933



## BACTERIAL ALLERGY

The delayed, inflammatory, tuberculin type of reaction which is obtained with ordinary bacterial products, with vaccines as well as with so-called bacterial proteins, has already been discussed. Of greater interest is the soluble specific substance, a carbohydrate of the bacterial cell which in specific cases is capable of eliciting an immediate urticarial reaction entirely comparable with the other skin reactions in clinical allergy. The most important recent article on the carbohydrate is that by Avery and Goebel,<sup>65</sup> the pioneers in the whole field, who were able to correlate the observations of others and greatly simplify the whole subject by finding that in the course of isolating the carbohydrate, treatment with dilute alkali results in the removal of the acetyl radical. Another method of extraction avoids the use of alkali and leaves the acetyl in place. The technic is of great importance because the acetyl carbohydrate is antigenic, and when used in the study of immune reactions, it absorbs the specific immune substances. On the other hand, the deacetylated material readily obtained by alkali is nonantigenic. It reacts actively and specifically with immune substances, but it absorbs these substances only in part. The difference between the two is great, but it is easily explained by a small detail in the process of extraction.

An important paper on another subject is that of King<sup>66</sup> on a tuberculin test of value in adults. King found that it is quite possible to standardize the activity of ordinary tuberculin so that a dilution of 1:20,000, for example, becomes the critical dilution which will give positive reactions in patients with active tuberculosis but will not react in normal persons or in those with inactive tuberculous disease. In a series of 225 cases, the results of his skin tests were in accord with the clinical diagnoses in 90 per cent.

## THE DIAGNOSIS OF HYPERSENSITIVENESS

This section is limited to the diagnosis of the cause of hay fever, asthma and eczema, which are characterized by an immediate urticarial reaction. Both the scratch method and the intradermal method of skin testing are widely used. O'Keefe and Burgin<sup>67</sup> compared the two, stating that of children with hay fever, 91 per cent gave satisfactory reactions when tested by the scratch method alone. Of children with

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65 Avery, O. T., and Goebel, W. F. Chemoimmunological Studies on the Soluble Specific Substance of Pneumococcus. I. The Isolation and Properties of the Acetyl Polysaccharide of Pneumococcus Type I, *J. Exper. Med.* **58**: 731, 1933.

66 King, Richard B. A Tuberculin Test of Value in Adults, *New England J. Med.* **207**: 831, 1932.

67 O'Keefe, E. S., and Burgin, L. B. Comparative Value of Scratch and Intradermal Methods of Skin Testing in Asthma and Hay Fever of Children, *New England J. Med.* **208**: 582, 1933.

asthma, however, only 30 per cent reacted to the scratch test, whereas the intradermal test brought the proportion of positive results up to 87 per cent

Tuft<sup>68</sup> studied the comparative value of intradermal and ophthalmic tests for sensitiveness to horse serum and concluded that the skin reaction is much more sensitive than the eye reaction and is less disturbing to the patient, especially if the patient is a child. In considering the use of skin tests, I must point out two vital discrepancies in every method. First, skin tests may be positive and yet have no clinical significance. For example, many patients with hay fever react to grass pollens just as strongly as to ragweed and yet have symptoms only in the ragweed season. Second, skin tests may be negative when the patient is sensitive. For example, several children have had symptoms of hay fever in season but have given quite negative reactions to skin tests. They have developed positive reactions later. The theoretical and practical importance of Stevens'<sup>46</sup> demonstrations of pulmonary sensitivity to inhaled substances in the face of negative skin reactions to the corresponding extracts has already been noted.

*Patch Test*—This test is new and represents the greatest recent practical advance in the clinical study of allergy. The skin sensitiveness which it represents has been discussed. The use of the test in the diagnosis of contact dermatitis, in which the lesions arise on exposed surfaces because of direct contact with the allergen, as opposed to allergic eczema, in which the cause is blood borne, was discussed by Sulzberger and Wise<sup>69</sup> in a very instructive article in 1931. Any number of substances can be tested, sometimes from 30 to 40 at once, and the test is positive in about 30 per cent of the cases. A more recent article of the same sort is that by Ayres and Anderson,<sup>70</sup> of Los Angeles, who presented good pictures of contact dermatitis and positive patch tests. A case report by Simon and Rackemann<sup>71</sup> illustrates the possibilities of the method. A special use of the patch test is in the diagnosis of obscure dermatids dependent on a sensitiveness to trichophyton infections as described by Sulzberger and Wise<sup>72</sup>. Incidentally, Jadassohn,

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68 Tuft, Louis. Comparative Value of Intradermal and Ophthalmic Tests for Sensitiveness to Horse Serum, *J Lab & Clin Med* **18** 1160, 1933

69 Sulzberger, M. B., and Wise, Fred. The Contact or Patch Test in Dermatology, *Arch Dermat & Syph* **23** 519 (March) 1931

70 Ayres, S., and Anderson, N. P. The Patch Test in the Diagnosis of Contact Dermatitis, *Ann Int Med* **6** 1161, 1933

71 Simon, F. A., and Rackemann, F. M. Contact Eczema Due to Clothing, *J A M A* **102** 127 (Jan 13) 1934

72 Sulzberger, M. B., and Wise, Fred. Ringworm and Trichophytin. Newer Developments, Including Practical and Theoretical Considerations, *J A M A* **99** 1759 (Nov 19) 1932

Schaaf and Sulzberger<sup>73</sup> were able to demonstrate the sensitiveness of the guinea-pig uterus by the Schultz-Dale technic after treatment of the animal with cultures of *Trichophyton*

*Urinary Protease*—A urinary protease with specific qualities isolated from the urine of patients with asthma and hay fever was described in 1928 by Barber and Oriel<sup>74</sup> The recent literature on the subject was carefully reviewed by Black and Shelmire,<sup>75</sup> who brought out the fact that in America, at least, the value of the protease as a specific test has been small and its importance questioned The chief difficulty seems to be that a similar protease can be isolated from many clinical conditions other than hay fever and asthma

*Sedimentation Rate*—The rate of sedimentation of red blood cells in uncomplicated hay fever was discussed by Gelfand and Victor,<sup>76</sup> who found that it remains normal before as well as during the season and quite regardless of specific treatment

*Leukopenic Index*—The leukopenic index is a new test devised by Vaughan<sup>77</sup> who checked the observations of the French on *colloidoclasie* and found that the total number of leukocytes does fall after the feeding of certain foods to which the patient is sensitive, and that the degree of fall and the degree of clinical sensitiveness are proportional to each other The method is of some value in the diagnosis of "food allergy"

*Clinical History*—The clinical history, however, remains above all as the best method of identifying the exciting cause of allergic symptoms, and it is surprising that no stress is laid on this important and practical point The history of an allergic patient should be taken by a detective rather than by a doctor! It should express the time of events, of changes in symptoms for better or worse, of changes in residence or of occupation by *exact dates* The season of the year, school vacations, travel and admissions to the hospital, when correlated with symptoms, will frequently reveal the cause of the trouble It is important to account for all the time in an effort to explain not only when and why the attack of asthma, eczema or migraine began, but also when and why it ended If the history is taken properly and carefully, skin tests will become almost unnecessary, and their chief function will be

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73 Jadassohn, W., Schaaf, F., and Sulzberger, M. B. Der Schultz-Dalesche Versuch mit *Trichophyton*, *Klin. Wchnschr.* **11** 857, 1932

74 Barber, H. W., and Oriel, G. H. A Clinical and Biological Study of Allergy, *Lancet* **2** 1064, 1928

75 Black, J. H., and Shelmire, B. The Urinary Protease in Allergy, *J. Allergy* **5** 373, 1934

76 Gelfand, B. B., and Victor, G. The Sedimentation Rate in Hay Fever, *J. Allergy* **5** 583, 1934

77 Vaughan, W. T. Food Allergens The Leucopenic Index Preliminary Report, *J. Allergy* **5** 601, 1934

to confirm the history and determine the degree of sensitiveness before the start of specific treatment

#### SEVERAL DIFFERENT CLINICAL MANIFESTATIONS OF ALLERGY

The separate discussion of hay fever, asthma, eczema and allied conditions is beyond the scope of a review of this kind. Perhaps they can be considered at a later time. There are, however, a number of topics which demand attention even in this limited space.

*Drug Allergy*—The allergy caused by ingestion of a drug is receiving attention and will receive more of it. The discovery by Madison and Squier<sup>78</sup> that primary agranulocytopenia is often due to a peculiar susceptibility to certain drugs, notably amidopyrine (they described the reaction as an allergic or anaphylactoid reaction), has led to a considerable discussion of the use and abuse of all the new sedative drugs and has drawn new attention to drug allergy. The recent papers by Short and Bauer<sup>79</sup> on cinchophen, Ford<sup>80</sup> on quinine, Meredith<sup>81</sup> on barbitol derivatives and Scheer and Keil<sup>82</sup> on codeine are typical.

*Sensitiveness to Tobacco*—This condition has a rather special interest because Harkavy<sup>83</sup> of Mount Sinai Hospital presented evidence to show that sensitivity to tobacco may have an important bearing in the etiology of thrombo-angitis obliterans and other vascular diseases. He finds that patients with these diseases show good skin reactions to tobacco whereas normal persons used as controls yield mostly negative reactions. Sulzberger<sup>84</sup> confirmed this work. His findings are of some interest. Intradermal tests with tobacco extracts produced immediate urticarial wheals in 36 per cent of smokers and in only 16 per cent of nonsmokers. Among adults with heart disease and in the general hospital population, the figures are 26 per cent and 28 per cent, respectively. On the other hand, of 13 patients with thrombo-angitis obliterans 10, or 77 per cent, showed positive reactions. In a more recent article,

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78 Madison, F. W., and Squier, T. L. Etiology of Primary Granulocytopenia (Agranulocytic Angina), *J. A. M. A.* **102** 755 (March 10) 1934.

79 Short, C. L., and Bauer, W. Cinchophen Hypersensitiveness. A Report of Four Cases and a Review, *Ann. Int. Med.* **6** 1449, 1933.

80 Ford, William K. Drug Eruption Due to Quinine. Recurrence Following Use of Contraceptive, *J. A. M. A.* **103** 483 (Aug. 18) 1934.

81 Meredith, Florence L. Reactions to Certain Barbitol Derivatives, *J. A. M. A.* **102** 2099 (June 23) 1934.

82 Scheer, M., and Keil, H. Skin Eruptions Due to Codeine, *J. A. M. A.* **102** 908 (March 24) 1934.

83 Harkavy, J. Tobacco Sensitiveness in Thromboangitis Obliterans, Migrating Phlebitis and Coronary Artery Disease, *Bull. New York Acad. Med.* **9** 318, 1933.

84 Sulzberger, M. B. Studies in Tobacco Hypersensitivity, *J. Immunol.* **24** 85, 1933.

Harkavy<sup>85</sup> presented the results of tests with the different kinds of tobacco extracts—Burly, Virginia and others

*Unusual Manifestations of Allergy*—First of all, Vaughan<sup>86</sup> urged that one distinguish between major and minor allergic manifestations. According to his figures, 10 per cent of the population have major allergy and are usually found sensitive to the more common or staple allergens. In contrast to this, he found that as many as 50 per cent gave a history of minor episodes which closely simulated more typical allergic manifestations. Transient eruptions of the skin, headache and gastro-intestinal disturbances of atypical character and occurring with considerable frequency, he found to depend on a sensitiveness, not to the staple allergens, but to the occasional and odd alleigens. Routine tests made on patients of this sort show a surprising incidence of queer reactions difficult to interpret on any other basis than that of minor allergy. The differences between the two groups are in his opinion more quantitative than qualitative. This work must be correlated with recent observations which my associates and I have made on skin tests in normal persons—that positive skin reactions are by no means uncommon even when no allergy of any kind is suspected.

*Migraine*—This disorder has not received its customary attention from the allergic point of view during the past year. In a special article, Bassoe<sup>87</sup> reviewed the subject from every angle and discussed the whole problem in a scholarly manner. Only half of one of his eleven columns is devoted to allergy as an important etiologic principle.

*Epilepsy*—This condition has been mentioned as of alleigic origin. Adamson and Sellers<sup>88</sup> found that the skin tests were positive in 30 per cent of 100 cases but that the transference of the skin reactions to the skin of normal persons was successful in only 10 of the cases, and even in these, it was not possible to show any clinical relation between the attacks and the particular foreign substance.

*Gastro-Intestinal Allergy*—This is another favored topic, important chiefly because the attack of gastro-intestinal allergy frequently simulates a surgical emergency and then leads to operation. Such a case was reported by Gallison,<sup>89</sup> who emphasized the importance of an eosinophilia

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<sup>85</sup> Harkavy, J. Skin Reactions to Tobacco Antigens in Smokers and Non-Smokers, *J. Allergy* **5** 131, 1934.

<sup>86</sup> Vaughan, W. T. Minor Allergy. Distribution, Clinical Aspects and Significance, *J. Allergy* **5** 184, 1934.

<sup>87</sup> Bassoe, Peter. Migraine, *J. A. M. A.* **101** 599 (Aug. 19) 1933.

<sup>88</sup> Adamson, W. B., and Sellers, E. D. Observations on the Incidence of the Hypersensitive State in One Hundred Cases of Epilepsy, *J. Allergy* **4** 315, 1933.

<sup>89</sup> Gallison, D. T. Gastro-Intestinal Allergy as a Cause of Intestinal Obstruction, *New England J. Med.* **211** 164, 1934.

of 8 per cent and the greater importance of the prompt and dramatic relief from all the symptoms following a hypodermic injection of epinephrine

*Cold Allergy*—Allergy due to cold is rare, but Paul<sup>90</sup> has demonstrated another typical case in which local urticaria was shown on application of cold water

*Arthus Phenomenon in Man*—This observation is rare, and the case reported by Ross<sup>91</sup> is of some interest. A small boy had been given diphtheritic toxin-antitoxin for immunization. A year later, he received tetanic antitoxin for an injury of the scalp. Three days later, a temperature of 104 F developed, and the symptoms so resembled scarlet fever that he was given an additional treatment with streptococcic antitoxin, injected into the buttock. Immediately, the site of injection became indurated and inflamed, and the lesion developed with such fulminating intensity that five days later the entire thigh, hip and abdomen were involved in a huge necrotic sloughing mass. The boy died that evening, nine days after the injection of the tetanic antitoxin.

*Anaphylactic Shock*—Incidentally, Waldbott<sup>92</sup> recently made a study of nine fatal cases of anaphylactic shock, in the last of which ragweed was the cause, the patient dying within two hours after the last dose of ragweed extract. Waldbott and Ascher,<sup>93</sup> too drew attention to what they call an "unusual reaction simulating allergic shock." This patient also was under treatment with ragweed and for no particular reason was seized with paroxysms of coughing, dyspnea and yawning following each of the doses. Later these symptoms became so severe that it was decided to discontinue the treatment. At that time, however, it was found that the injection of physiologic solution of sodium chloride without the patient's knowledge would produce the same clinical picture. As Waldbott stated, this case offers an excellent demonstration of the fact that attacks of "asthma nervosum" may be practically identical with those of allergic asthma.

#### TREATMENT OF HAY FEVER

The treatment of hay fever must depend primarily on an accurate knowledge of the pollens in the particular district. The American

90 Paul, Lee W. Cold Allergy, J A M A **103** 24 (July 7) 1934

91 Ross, Fred E. The Arthus Phenomenon. Report of a Case, J A M A **103** 563 (Aug 25) 1934

92 Waldbott, George L. The Prevention of Anaphylactic Shock with a Study of Nine Fatal Cases, J A M A **98** 446 (Feb 6) 1932

93 Waldbott, George L., and Ascher, M. S. Unusual "Reaction" Simulating Allergic Shock, J A M A **102** 127 (Jan 13) 1934

Association for the Study of Allergy is fortunate to have the services of Mr O C Durham available to its members. His work is good. In 1933, he gave information about the plants of Canada<sup>94</sup> and of Chicago<sup>95</sup> that cause hay fever and added<sup>96</sup> an interesting discussion of those pollens which may overlap into the neighboring districts to complicate the local pollen incidence.

From the Southwest, Lamson and Watry<sup>97</sup> described the sages, thistles and junipers which cause hay fever in northern Arizona.

The treatment of hay fever is by elimination and by desensitization particularly.

*Air Filtration*—This measure and air conditioning have suggested various studies. Gay<sup>98</sup> of Johns Hopkins University, with the cooperation of the General Motors Corporation, has been able to work with a very efficient room "air conditioned" with frigidaire.

Nelson, Rappaport and Welker<sup>99</sup> had a similar opportunity in Chicago, and Vaughan and Cooley<sup>100</sup> have used the method in Richmond. These studies seem to show that patients with hay fever vary considerably in their response to cool and dust-free air. Some of them lose their symptoms in a few minutes, others, however, require from one to two hours before relief comes. On going back to the outer world, symptoms may return promptly, or the patient may be comfortable for a time, usually a few hours, but the time is not long, and the symptoms are prone to recur. The original hope that if the patient could return to the air-conditioned room each night and be outside of it for only from eight to ten hours a day he would remain relatively free from symptoms is not sustained. Such an intermittent residence in the ward will not prevent hay fever.

*Desensitization or Specific Treatment*—This treatment in hay fever varies in technic according to the number of doses and the time between

94 Durham, O C. Fall Hay Fever Pollens of Canada, *Canad M A J* **28** 604, 1933.

95 Feinberg, S M, and Durham, O C. Hay Fever in Chicago and Suburbs. Clinical, Field, and Air Observations, *Illinois M J* **63** 464, 1933.

96 Durham, O C. Complicating Pollen Factors Encountered in Ragweed Hay Fever, An Atmospheric Study, *J A M A* **100** 1846 (June 10) 1933.

97 Lamson, R W, and Watry, A. Survey of a Botanic Oasis in the Desert of Northern Arizona, *J Allergy* **5** 389, 1934.

98 Gay, L N. The Treatment of Hay Fever and Pollen Asthma by Air-Conditioned Atmosphere, *J A M A* **100** 1382 (May 6) 1933.

99 Nelson, T, Rappaport, B Z, and Welker, W H. The Effect of Air Filtration in Hay Fever and Pollen Asthma. Further Studies, *J A M A* **100** 1385 (May 6) 1933.

100 Vaughan, W T, and Cooley, L E. Air Conditioning as a Means of Removing Pollen and Other Particulate Matter and of Relieving Pollenosis, *J Allergy* **5** 37, 1933.

them as well as according to the route by which the doses are given. The question of perennial versus preseasonal treatment has been debated extensively. A good survey of the literature is by Unger,<sup>101</sup> who added the figures on his own results to show that results are infinitely better with the perennial than with the preseasonal method. The route by which the doses should be given is an interesting problem in view of the work of Kahn,<sup>47</sup> referred to in the discussion on desensitization. Phillips<sup>102</sup> reported that he gave his patients doses every day and injected all of them intradermally, saying that an average series of 14 doses was quite sufficient to obtain striking relief in a large proportion of the cases. This is interesting because in animal experiments repeated intradermal doses increase the sensitiveness of the skin. Theoretically, desensitization should be obtained best by treatment which is given intravenously. This would be the method of choice if the main object were to produce a true immunity. Lichtenstein<sup>103</sup> tried the method and treated 6 patients, all sensitive to ragweed, with intravenous doses of various dilutions, the exact amount being made up to about 15 cc with salt solution. His patients were given from 1 to 15 treatments. Every patient had one or more reactions varying in character, but all of them did well. The fact is interesting and the idea needs further consideration.

The latest treatment for hay fever is that reported by Warwick<sup>104</sup> who employs nasal ionization using a metallic electrode and salts of the same metals. He precipitates the metal on the nasal mucous membrane by means of a suitable direct current. He made the claim that no damage is done to the nose, and that after a slight reaction the patients are better of their hay fever and are rendered less susceptible to head colds later on. The method is being used in many clinics at the present time.

*Pollen Treatment*—The results of this treatment may often be reflected by a reduction in the size of skin reactions, according to Colmes and Rackemann,<sup>105</sup> but the rule is not absolute, for good results occurred without change in the size of the skin reactions in 18 per cent of their cases, and poor results occurred in 11 per cent in spite of the fact that in this group the skin reactions were smaller after the treat-

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101 Unger, L. Perennial Versus Preseasonal Treatment of Hay Fever, *J Allergy* **3** 531, 1932.

102 Phillips, E. W. Intradermal Pollen Therapy During the Attack, *J Allergy* **5** 29, 1933.

103 Lichtenstein, M. R. Intravenous Pollen Therapy, *J Allergy* **5** 230, 1934.

104 Warwick, H. L. Desensitization of Nasal Mucous Membranes for Relief of Hay Fever, Asthma and Food Allergy, *Laryngoscope* **44** 173, 1934.

105 Colmes, A., and Rackemann, F. M. Further Observations on the Changes in Skin Tests Following Specific Pollen Therapy, *J Allergy* **4** 473, 1933.



ment than before. It seems that relief from symptoms and reduction in reactions could hardly depend on a common basis. Markow and Spain<sup>106</sup> had a similar experience, although they reported that a diminution in the size of skin reactions did not occur in many of their cases and that when it did, it was seen only after several years of treatment.

*Clinical End-Results*—Feinberg<sup>107</sup> was wise in urging that the experiences of the individual patient be compared with those of the particular group to which the patient belongs, for, as he pointed out, the severity of the pollen season changes from year to year, and the results of treatment in any one case must be interpreted according to this general change.

Walker<sup>108</sup> expressed the belief that hay fever is curable. Of his total of 734 patients, 190, or 26 per cent, had remained free from symptoms for three years or over. His figures show that each succeeding year of preseasonal treatment increases the chance of a permanent result.

#### STUDIES IN ASTHMA

Studies in asthma are numerous. The most important recent progress concerns the relation of lesions of the nose and throat to asthma. There are three excellent papers. Kern and Schenck's<sup>109</sup> paper contains an excellent review of the preceding literature. Their work concerns mucous polyps, which they found to be extremely common in allergic conditions but comparatively rare in patients with nonallergic diseases, even in those patients who have extensive and chronic sinus infection. In their experience, all patients with mucous polyps have a personal history of allergy, and they declared that the finding of mucous polyps warrants the assumption that the patient is of allergic strain and should be studied from the standard of clinical hypersensitiveness.

Grove and Cooke<sup>110</sup> studied the cultures and tissues taken at operation from patients with chronic hyperplastic sinusitis. Eosinophilic infiltration was the rule, and organisms were present in 85 per cent of their specimens. In their experience, it is unusual to find polyp or even

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106 Markow, H., and Spain, W. C. The Effect of Consecutive Years of Treatment upon Cutaneous Sensitiveness in Late Hay Fever, *J. Allergy* **4** 363, 1933.

107 Feinberg, Samuel M. A Method of Evaluation of Results in Hay Fever, Its Application to Certain Modes of Treatment, *Ann. Int. Med.* **6** 1153, 1933.

108 Walker, I. C. Curability of Hay Fever, *Arch. Int. Med.* **54** 289 (Aug.) 1934.

109 Kern, R. A., and Schenck, H. P. Allergy a Constant Factor in the Etiology of So-Called Mucous Nasal Polyp, *J. Allergy* **4** 485, 1933.

110 Grove, R. C., and Cooke, R. A. Etiology and Nature of Chronic Hyperplastic Sinusitis, *Arch. Otolaryng.* **18** 622 (Nov.) 1933.

chronic thickening of the sinus membrane without a complicating infectious process. Of 175 patients with infective allergy, 48 per cent showed definite polyp formation. It is in some of these patients that vaccines produce violent constitutional reactions.

Weille<sup>111</sup> operated on 40 patients with asthma who suffered from chronic sinus disease, and he followed all of them very carefully for at least a year and some of them for five or six years. Following operation, temporary cure was common, but permanent cure occurred in only 5 of the 40 cases, with 9 in which the condition was markedly improved. Weille stated that patients with polyp formation or with purulent cystic degeneration are the most favorable for operation, whereas those with purely extrinsic causes, whose asthma depends on hypersensitiveness to foods or dusts, receive no benefit from surgical intervention. Somewhat paradoxical is his observation of several patients who were relieved of their asthma as well as of their sinusitis even though only one side of the nose was operated on. Another paradox was the finding that operation caused a marked improvement in the nasal condition but did not affect the asthma. Knowledge of the relation of chronic infection to asthma is still faulty, but physicians are learning.

At the end of this survey, I should like to call attention once more to what I believe are the fundamental problems in allergy. First, the function and the purpose of the allergic reaction must be understood. Evidence has been presented to show that it represents a phase of the process of immunity. It is obvious that if the mechanism could be understood accurately, the treatment of hay fever, for example, would be understood and then the results would always be satisfactory. A second problem concerns the so-called allergic or atopic state—whether those patients whom one regards as “typically allergic” are really different from normal persons or whether the apparent variations depend merely on a quantitative change. A third problem concerns the mechanism of the production of symptoms, as, for example, in asthma of the severe, intractable type. Is there an excess of some poisonous substance or is there, perhaps, a lack of some protective mechanism which is present in normal persons? It is to be hoped that the investigations to be described during the coming year will help in the solution of these problems.

Meantime, the substances found to elicit one or other symptoms of allergy are in great and increasing variety. The following list of references to new allergens will indicate the scope of the subject and will show why the list of possibilities can never be closed.

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<sup>111</sup> Weille, Francis L. Studies in Asthma. XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, *J. A. M. A.* **100** 241 (Jan. 28) 1933.

## REFERENCES TO NEW ALLERGENS

*The offending substance caused allergy of the immediate atopic type and gave urticarial skin reactions*

- Adkinson and Walker, I C A Patient Sensitized to an Art Gum Eraser, J A M A **101** 2117 (Dec 30) 1933
- Baagøe, K Mehlidiosynkrasie als Ursache von vasomotorischer Rhinitis und Asthma, Ugesk f læger **95** 513, 1933
- Bennett, Richard H, and Schwartz, Emanuel Castor Bean Dust Sensitization, J Allergy **5** 427, 1934
- Duke, W W Sensitiveness to Corn Shuck, J A M A **99** 468 (Aug 6) 1932
- Feinberg, S M Pyrethrum Sensitization, J A M A **102** 1557 (May 12) 1934
- and Aries, P L Asthma from Food Odors, J A M A **99** 2280 (June 25) 1932
- Hollander, Lester Urticaria Due to Senna Leaves, J A M A **100** 1329 (April 29) 1933
- Idiosyncrasy to Quinine, Queries and Minor Notes, J A M A **101** 731 (Aug 26) 1933
- Parlato, S J Emanations of Flies as Exciting Causes of Allergic Coryza and Asthma, J Allergy **3** 459, 1932
- LaDuca, P J, and Durham, O C Studies of Hypersensitiveness to the Emanations of the Caddis Fly (Trichoptera), Ann Int Med **7** 1420, 1934
- Randolph, Howell Allergic Response to Dust of Insect Origin, J A M A **103** 560 (Aug 25) 1934
- Taub, Samuel J Allergy Due to Silk, J Allergy **1** 539, 1930
- Cottonseed Allergy, J A M A **103** 334 (Aug 4) 1934

*The offending substance caused immediate symptoms, but skin tests were either negative or were not made*

- Allergic Reaction to Honey, Queries and Minor Notes, J A M A **101** 728 (Aug 26) 1933
- Lamson, R W, and Thomas, R Some Untoward Effects of Acetyl-Salicylic Acid, J A M A **99** 107 (July 9) 1932
- Spielman, A D, and Baldwin, H S Atopy to Gum Arabic (Causing Asthma), J A M A **101** 444 (Aug 5) 1933
- Watson, S H, and Kibler, S C [Chlorine in] Drinking Water as a Cause of Asthma, J Allergy **5** 197, 1934

*The offending substance caused a dermatitis and gave a positive patch test*

- Cummer, Clyde L Dermatitis from the Use of Hexylresorcinol Solution, S T **37**, Acquired Sensitivity, J A M A **100** 884 (March 25) 1933
- Downing, J G Dermatitis from Rubber Gloves, New England J Med **208** 196, 1933
- Eades, M F Dermatitis of the Breasts Caused by Compound Tincture of Benzoin Report of Three Cases, New England J Med **211** 632 1934
- Fowlkes, R W Dermatitis Due to Nupercaine, J A M A **100** 1171 (April 15) 1933
- Fox, Howard Nickel Dermatitis from Spectacle Frames and Wrist Watch, J A M A **101** 1066 (Sept 30) 1933
- French, S W A Case of Skin Sensitivity to Parthenium Hysterophorus, Mil Surgeon **66** 623 (May) 1930
- Grant, L R Flaxseed Sensitization with Review of Literature, J Allergy **3** 469, 1932

- Henry, S A Celery Itch Dermatitis Due to Celery in Vegetable Canning,  
Brit J Dermat **45** 301, 1933
- Hollander, Lester Dermatitis of the Upper Eyelids Due to the Use of a "Hair  
Tonic" (Wildroot), J A M A **97** 1384 (Nov 7) 1931
- Levin, Oscar L Sawdust Dermatitis, J A M A **100** 570 (Feb 25) 1933
- Senear, Francis E Dermatitis Due to Woods, J A M A **101** 1527 (Nov 11)  
1933
- Sulzberger, M B, and Weinberg, C B Dermatitis Due to Insect Powder, J A  
M A **95** 111 (July 12) 1930
- The offending substance caused severe dermatitis, but patch tests were negative*
- Baer, Harry L A Dermatitis Due to Aniline Dye in a Food Product, J A  
M A **103** 10 (July 7) 1934
- Langenbach, Alfred, M Acquired Sensitization to Sodium Iso-Amylethylbarbitu-  
rate (Sodium Amytal) as Evidenced by Cutaneous Eruptions Report of 4  
Cases, J A M A **102** 1376 (April 28) 1934
- Matzger, Edward Can Sensitivity to Dinitrophenol Be Determined by Skin Tests?  
J A M A **103** 253 (July 28) 1934
- 263 Beacon Street, Boston

## News and Comment

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### ATLANTIC CITY SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Section on Practice of Medicine of the American Medical Association has appointed the following section exhibit committee for the Scientific Exhibit at the Atlantic City session of the American Medical Association and the Canadian Medical Association: Irving S. Wright, New York, chairman, Russell L. Haden, Cleveland, Eugene S. Kilgore, San Francisco, L. G. Rowntree, Philadelphia, and D. Sclater Lewis, Montreal, Canada. Application for space must be made by Feb. 25, 1935. Application blanks may be obtained from any of the members of the committee or from the Director, Scientific Exhibit, 535 North Dearborn Street, Chicago.

### ACADEMIA NACIONAL DE MEDICINA DE MEXICO

The following officers of the Academia Nacional de Medicina de Mexico were recently elected: Dr. Francisco de P. Miranda, president, Dr. Gustavo Baz, vice-president, Dr. Alfonso Pruneda, permanent secretary, Dr. Miguel E. Bustamante, annual secretary, and Dr. Ramon Pardo, treasurer.

## Book Reviews

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**A Textbook of Histology Functional Significance of Cells and Inter-cellular Substances** By E V Cowdry, Professor of Cytology, Washington University School of Medicine Price, \$5 50 Pp 503, with 242 illustrations Philadelphia Lea & Febiger, 1934

Departing from the conventional approach in the didactics of histology, Cowdry builds up the subject with the vascular system as a central theme. The first chapter is devoted to an introductory consideration of the body fluids—tissue fluid, blood and lymph—touching on the physiologic import of these mediums. Cowdry then proceeds with a detailed discussion of blood (sixty-three pages), followed by separate chapters on the blood vessels and the heart, the whole being emphasized as a “principal integrator” system. Lymphatic vessels and the chief lymphoid organs are next considered, with a view to their functional relationships with this integrator system, the endocrines are next discussed as agents of “chemical integration.” The digestive system is likewise aligned with the vascular mechanism, as a provision for the “intake of water, nutriment, accessory food factors and removal of waste.” The respiratory system is as naturally emphasized for its rôle in “oxygen consumption and carbon dioxide elimination,” and the urinary system is discussed as the agent for “regulation of constitution of blood and removal of waste.” The nervous system is contrasted with the vascular system in mediating “rapid integration.” The next chapters consider the connective and muscular systems as the means of “architectural support” and the reproductive system for “perpetuation of the race,” concluding with a consideration of the skin, which serves for “unification, protection and adjustment.” As these headings indicate, the treatment is distinctively physiologic throughout, and a direct, lively style adds forcefulness and interest. The book may be recommended to those who desire a reference work on modern physiologic histology more compact than the three-volume “Special Cytology” edited by the same author. In keeping with his plan, Cowdry has not followed the tradition of proceeding successively from cell structures to systematic description of elementary tissues, organs and systems. He has omitted figures which would only “show at a glance what the actual preparations will lead the students to discover for themselves,” with the result that but few illustrations of routine histologic sections appear. Favorably impressed as they may be by the vivification of histology afforded by this book, some teachers of the subject will doubtless consider it ill-adapted in other respects as a text for the average beginning medical student.

**Tuberculosis in the Child and the Adult** By Francis Marion Pottenger, A M, M D, L L D, F A C P Price, \$8 50 Pp 611, with 85 illustrations St Louis C V Mosby Company, 1934

This excellent monograph represents the recording of the experiences and the studies of many years of a well known specialist in the field of pulmonary tuberculosis. The occurrence of tuberculosis in childhood and the subsequent relation that this disease bears to tuberculosis in adults is clearly presented. A detailed discussion is given of the body's reaction to the tubercle bacillus in respect to cell sensitization and immunity. The effects of remoculation on the mechanism of immunity are emphasized, and it is shown that the clinical picture varies according to the several immunity reactions.

The mechanism of symptoms is explained on a visceroneurologic basis. Pottenger has divided the symptoms into three groups: those due to toxemia, those due to reflex stimulation and those due to the tuberculous process per se. The diagnosis of tuberculosis is given thorough consideration, with a careful

appraisal of each diagnostic procedure. The various types of tuberculosis are illustrated by roentgenograms. The author emphasizes the advantages of the dilution-flotation-trinitrophenol method over the usual methods of examining for tubercle bacilli.

The complications of the disease are discussed in a thorough manner as regards the diagnosis, prognosis and treatment.

The principles of treatment are comprehensively presented. It is suggested that the technic in the employment of therapeutic measures be comparable to that in surgical procedures. The importance of tuberculin in treatment is convincingly brought out. A thorough and practical discussion is given on the indications, contraindications and results of the various forms of compression therapy.

The latter part of the book is devoted to diagnostic and therapeutic principles, with reports of illustrative cases and roentgenograms.

This book should be a gratifying addition to any student's or physician's library.

**The Harvey Lectures, 1932-1933** Pp 233 Baltimore The Williams & Wilkins Company, 1934

This volume, issued by the Harvey Society, contains a number of significant lectures constituting reviews of important subjects in chemical and metabolic phases of medicine. Dr Julius Bauer, professor of clinical medicine of the University of Vienna, contributes a review, "The Constitutional Principle in Clinical Medicine." Dr L. O. Funkel, a member of the department of animal and plant pathology of the Rockefeller Institute for Medical Research, describes "The Similarities Between the Diseases of the Vegetable Kingdom and Those of Man and Animals." Dr George W. Corner, professor of anatomy of the University of Rochester, reviews the recent interesting evidence regarding "The Nature of the Menstrual Cycle." Then follows a seventy page paper by Dr Harvey Cushing, "Dyspituitarism Twenty Years Later." In this he gives particular attention to the syndrome which he now calls pituitary basophilism. Following is a lecture by Dr James B. Conant, professor of chemistry, Harvard University, "The Oxidation of Hemoglobin and Other Respiratory Pigments." This is followed by "Contributions of Chemistry to the Knowledge of Immune Processes" by Dr Michael Heidelberger, associate professor of biologic chemistry, Columbia University. Then there is a discussion, "Recent Biochemical Studies of Liver Function," by Dr J. C. Drummond, professor of physiology and biochemistry, University College, London. The volume is completed by a lecture "Humoral Transmission of Nervous Impulses" by Dr Otto Loewi, professor of pharmacology, the University of Graz, Austria, the pioneer in this field through his discovery of the so-called *Vagusstoff*.

A careful perusal of this volume will prove very much worth while to every physician attempting to keep abreast in this important humoral field of internal medicine.

**L'Infarctus du myocarde** Etude expérimentale, électrocardiographique, et clinique. By Eduardo Coelho, Professeur a la Faculte de Medecine, Medecin de l'Hôpital de Santa Marta, Lisbonne. Paper. Price, 35 francs. Pp 212, with 105 figures and illustrations. Paris. Masson & Cie, 1934.

This work shows the result of careful and painstaking observation on the effect of obstruction of the coronary circulation. The subject is considered from the experimental and clinical sides, is well treated, succinctly set forth and accompanied by a fairly comprehensive bibliography.

The first portion of the book is devoted to a review of the anatomy of the coronary circulation. Diagrams and photographs assist the reader in visualizing this.

In the experimental production of coronary occlusion several methods were used. Ligature, before and after section of the vagus and sympathetic nerves, was employed to obstruct various branches of the coronary arteries. Infarction was

produced in numerous places by the use of alcohol and silver nitrate, and, lastly, embolic infarction was caused by iodized poppy-seed oil 40 per cent, charcoal and lycopodium powder

The immediate and ultimate effect of these procedures is discussed in relation to the electrocardiogram and to the mortality in experimental animals

The clinical consideration of coronary occlusion is developed by a discussion of twenty-eight cases, with observations at autopsy, and these are correlated with the experimental work. Electrocardiograms are shown or described in all the cases

Finally, the clinical cases are tabulated in relation to the common clinical symptoms and findings in this disorder

**Die Zuckerkrankheit** By Ferdinand Bertram Price, 5 80 marks Pp 94, with 15 illustrations Leipzig Georg Thieme, 1934

After reviewing in a reasonably satisfactory and brief manner the current views on the pathogenesis of diabetes, Bertram proceeds to outline the method of treatment found effective in the Hamburg clinic. The dietary measures described will not be very useful for the American practitioner. They are complicated, as compared with American plans, and the type of foods called for and the frequent meals are foreign to American food habits

Bertram's strenuous objection to the patient's testing his urine leaves the reviewer with the impression that the very corner-stone of good treatment is neglected in Hamburg. With no knowledge by the patient of the state of his urine, it becomes almost impossible for him to regulate his dose of insulin. The objection is based on the fear that the patient will be disturbed psychologically if he is constantly watching his urine, but this is seldom found to be the case in the larger American clinics. Bertram prefers to have his patients excrete sugar in amounts of at least from 10 to 20 Gm daily. He maintains that the majority of them feel healthier under such circumstances. The reviewer disagrees with this. It is admitted that overly rigid treatment, such as may be required to bring the blood sugar to a normal level, is to be avoided, especially in cases complicated with arteriosclerosis. The danger of insulin treatment in patients with heart disease, especially with hypertension and coronary sclerosis, must not be minimized, but it is not as serious, in the reviewer's opinion, as is suggested by this book. The reviewer has seen a few cases in which anginal pain could be produced by over-rigid treatment, but careful inquiries as to the experience of the larger American clinics in this matter has revealed very few deaths attributable to this cause

**Clinical Pathology of the Jaws** By Kurt H Thoma, D M D, Professor of Oral Pathology in Harvard University Price, \$9 Pp 643, with 423 illustrations Springfield, Ill Charles C Thomas, Publisher, 1934

Thoma states that this volume was written to describe in detail special work in a special field and particularly to correlate the pathologic changes that are encountered in that field with the clinical expression of disease. This aim has been accomplished most successfully

Diseases of the jaw are discussed from a variety of angles. Malformations, fractures, infections, endocrine disturbances and tumors, benign and malignant, primary or metastatic, are depicted as they involve the jaw. Each phase of diseases of the jaw is well described clinically and pathologically, brief reports of cases are frequently interpolated and help to enliven the text, the illustrations are clear and helpful, and at the end of each chapter are those references to the literature which the author considers most significant in regard to the topic under discussion

A wealth of material has been analyzed and sorted out to make up this book. Thus the volume as a whole is very complete. Surgeons, internists, radiologists and dentists will find much of common interest in it and will be glad to have it on hand for reference in their attack on the many diverse clinical states that may involve the jaw



**Hygiene for Freshmen** By Alfred Worcester, A M , M D , Sc D Price, \$1 50  
Pp 151 Springfield, Ill Charles C Thomas, Publisher, 1934

The business of teaching hygiene, that is to say, elementary medicine, to laymen is at best a difficult matter How shall one make the subject at all intelligible to those who have not the underlying scientific knowledge? How shall one preserve a proper balance so as not to create perplexities, doubts and phobias? How avoid the danger inherent in "a little knowledge"? The present compendium seems to achieve its end fairly well within these limits Two sections, however, stimulate the reviewer to make certain comments The teaching of the hygiene of exercise is cautiously worded so as not to conflict too blatantly with the obviously unhygienic practices tolerated in certain branches of athletics One finds no comment on whether it is good or bad for the body and mind to have young men pounded and beaten on the football field or to have them collapse over their oars at the end of a boat race The statement is merely made that "No boat race can ever be won by a crew just after dining" So, too, in the passages on sex hygiene, one discovers under an outer show of frankness the same old evasions It is a question whether sex problems should be dealt with in books at all The circumstances are different in each case and can be solved adequately only by individual conferences At any rate, let one hope that some day this problem will be discussed with freshmen from the purely physiologic and medical standpoint without sinister and sanctimonious overtones

**Functional Disorders of the Large Intestine** By Jacob Buckstein Price, \$3  
Pp 265, with 60 drawings and 40 roentgenograms New York Harper & Brothers, 1934

Buckstein has compiled a concise, readable review of the functional disorders of the bowel, which is enriched not only by a comprehensive bibliography but also by his own wide experience in this field As in former works by this author, there are many excellent illustrations, particularly the series of roentgenograms Details of diets and exercises, which in many books are left to one's imagination, are included

The author has summarized various opinions on such subjects as ileal and cecal stasis, enteroptosis, intestinal flora and autointoxication The text leaves one with the impression that such conditions may cause more trouble than is usually held by many workers in this field It is regrettable that colonic irrigations for mucous colitis should be included in the discussion of treatment, although in another section routine irrigation is properly condemned Probably for completeness, various types of diarrhea are included, but necessarily too briefly for the author to do them justice In the discussion of sprue, for instance, mention of the use of liver in treatment has been omitted

**Leitfaden der einheimischen Wurmkrankheiten des Menschen** By L Szidat and R Wigand Price, 15 50 marks Pp 212, with 156 illustrations  
Leipzig Georg Thieme, 1934

This monograph, without claiming originality, deals in a concise and readable form with the common animal parasites of man and the diseases caused by them The format is excellent, and the many splendid illustrations are an outstanding feature The American reader, educated by the work of the Council on Pharmacy and Chemistry of the American Medical Association, is shocked at the emphasis placed on proprietary pharmaceuticals, such as filmaron, gelodurat, helminal, butolan, oylax, oymors, oxural and wurmserol Owing to absence of an index, the book is difficult to use for reference

## RELATIONSHIP BETWEEN RHEUMATIC AND SUBACUTE BACTERIAL ENDOCARDITIS

WILLIAM C VON GLAHN, M D

AND

ALWIN M PAPPENHEIMER, M D

NEW YORK

It is well known that a heart once damaged by rheumatic disease is more liable to subsequent infection, especially with nonhemolytic streptococci. In a review of 330 cases of subacute bacterial endocarditis, Blumer<sup>1</sup> found that 168, or 50 per cent, of the patients had a definite history of rheumatism (140), chorea (10) and tonsillitis (18). In 20 cases of streptococcus viridans endocarditis that were analyzed by Thayer<sup>2a</sup> and that came to necropsy, 65 per cent of the patients had a history of rheumatism or chorea.<sup>2b</sup> In a survey of 115 cases of subacute bacterial endocarditis collected from the records of the Presbyterian Hospital (New York), Lamb<sup>3</sup> noted 94 patients (82 per cent) who were known to have had cardiac damage, and of these, 69, or 60 per cent of the entire series, gave a history of rheumatism. In a group of 111 cases of subacute bacterial endocarditis studied by Fulton and Levine<sup>4</sup> 50 of the patients had a history of previous rheumatism. The most recent studies of rheumatic fever (White and Jones<sup>5</sup>) indicated that 41 per cent of the patients (39 of 956) later succumbed to subacute endocarditis.

These citations will suffice to indicate the general frequency of the association of the two diseases.

While there is thus abundant statistical evidence for a relation between rheumatic fever and subacute bacterial endocarditis, various conceptions may be held as to the nature of this relationship. (1) The lesions of rheumatic and bacterial endocarditis are reactions of different

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From the Department of Pathology, College of Physicians and Surgeons, Columbia University

1 Blumer, G. Subacute Bacterial Endocarditis, *Medicine* **2** 105, 1923

2 (a) Thayer, W. S. Studies on Bacterial (Infective) Endocarditis, *Johns Hopkins Hosp Rep* **22** 1, 1926, (b) p 84, (c) p 15

3 Lamb, A. R. Personal communication to the authors

4 Fulton, M. M., and Levine, S. A. Subacute Bacterial Endocarditis with Special Reference to the Valvular Lesions and Previous History, *Am J M Sc* **183** 60, 1932

5 White, P. D., and Jones, T. D. Heart Disease and Disorders in New England, *Am Heart J* **3** 302 (Feb) 1928

intensity to the same infection, or (2) subacute bacterial endocarditis is a secondary infection, superimposed on (a) old or healed rheumatic valvular lesions or (b) recent or active rheumatic vegetations. It is this last theory, so little stressed in the literature, that we wish to substantiate with evidence gathered from a close study of our material obtained at necropsy. It may be well, however, to cite in detail the views of recent workers in support of each of these possibilities.

The view that both processes represent reactions of different intensity to the same causative agent (streptococci) is maintained by Clawson and Bell,<sup>6a</sup> who have been impressed with the frequency with which the two types of lesions are found in the same heart. In their words,

From a study of a large number of cases, we get the impression that these two forms of endocarditis represent mild and severe degrees of the same infection.<sup>6b</sup>

Histological studies of the valve leaflets indicated also that the two forms of endocarditis differ only in the intensity of the inflammatory process.<sup>6c</sup>

In their summary, they stated again

In both types there is a proliferative inflammation in the valve, but the thrombus over the infected area is larger and softer in the subacute lesion. The streptococci, generally the viridans strain, seem to be responsible for both rheumatic and subacute bacterial endocarditis.

Clawson, Bell and Hartzell<sup>7a</sup> expressed the same point of view when they stated, in reference to the commonly observed transition between the two types of lesions

Unless the improbable assumption is made that three-fourths of the subacute bacterial cases have a simultaneous rheumatic infection, it must be granted that rheumatic and bacterial endocarditis are caused by the same organism.<sup>7b</sup>

In a recent review of the Aschoff nodule, Clawson<sup>8</sup> again emphasized the frequency with which proliferative inflammation of the valves like that found in acute rheumatic endocarditis, occurs in cases of subacute bacterial infection. He again drew the conclusion that this association, as well as the frequently found Aschoff nodules in the myocardium (45 per cent of 60 cases), indicated a common etiology.

Jaffe<sup>9a</sup> also described noninfected verrucae and subendothelial cell palisades occurring side by side with vegetations containing bacteria and composed of thrombotic deposits, necrotic tissue, giant cells and wandering cells of various types. Without committing himself definitely on

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6 (a) Clawson, B. J., and Bell, E. T. A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, *Arch. Int. Med.* **37**: 66 (Jan.) 1926, (b) p. 67, (c) p. 79.

7 (a) Clawson, B. J., Bell, E. T., and Hartzell, T. B. Valvular Disease of the Heart with Special Reference to the Pathogenesis of Old Valvular Defects, *Am. J. Path.* **2**: 193 (May) 1926, (b) p. 230.

8 Clawson, B. J. The Aschoff Nodule, *Arch. Path.* **8**: 664 (Oct.) 1929.

9 Jaffe, R. H. (a) Zur Histologie der Herzklappenveränderungen bei der Endocarditis lenta, *Virchows Arch. f. path. Anat.* **287**: 379, 1932, (b) p. 391.

the question of the etiology, he said that these observations can be interpreted in the sense of a causal relationship between endocarditis lenta and rheumatic endocarditis ("Können auch die hiermitgeteilten Befunde im Sinne einer ursächlichen Verwandtschaft zwischen lenta und rheumatischer Endokarditis gewertet werden <sup>9b</sup>)

These quotations will serve to illustrate the point of view of the investigators who, struck by the frequency of this association, deduce a common streptococcic origin

The second theory, that the bacterial vegetations are engrafted on valves *previously* damaged by rheumatic disease is the one usually given. Thus Coombs <sup>10</sup> stated that "these forms of valvular infection (i e., endocarditis lenta) often arise on a basis of old valvular sclerosis of rheumatic infection" Ribbert <sup>11</sup> declared

Mit besondere Vorliebe entwickelt sich die maligne Endocarditis auf schon pathologisch veränderten Klappen. Daher sind ihre Prädilektionsstellen arteriosklerotische Klappenläsionen oder alte rheumatische Klappenverdickungen (Malignant endocarditis develops especially on pathologically altered valves. The sites of predilection are therefore arteriosclerotic lesions of the valves or old rheumatic thickenings.)

Thayer stated

It is difficult to escape the conclusion that the frequent involvement of the wall of the left auricle in subacute streptococcus endocarditis is dependent on the same predisposing causes as in the case of the valves themselves—namely, the existence of scarred and sclerotic areas, the result of preceding rheumatic disease, these areas seem to be especially vulnerable <sup>2c</sup>

Swift stated

The bacterial endocarditis is practically always secondary, in other words, the bacteria are implanted in or on an abnormal valve, and in the majority of instances, the valve has been the seat of an old rheumatic endocarditis <sup>12</sup>

MacCallum <sup>13</sup> said

It seems probable that many of the cases of bacterial endocarditis arise because the valves have been injured by rheumatic infection

And again,

We have observed in rheumatism a peculiar patch of thickening of the wall of the left auricle which ends in the formation of a puckered scar there, and in the cases of streptococcus viridans endocarditis this same place forms the site of vegetations in very many cases

10 Coombs, C F Rheumatic Heart Disease, New York, William Wood & Company, 1924, p 31

11 Ribbert, H Die Erkrankungen des Endokards, in Henke, F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol 2, p 223

12 Swift, H The Heart in Infection, Am Heart J 3 12, 1928

13 MacCallum, W G Textbook of Pathology, ed 5, Philadelphia, W B Saunders Company, 1932, pp 237 and 504

In discussing the relation of rheumatism to subacute bacterial endocarditis, Boyd<sup>14</sup> said, "We know that subacute endocarditis very frequently develops on top of a previous rheumatic lesion"

The third possibility, that the bacteria are implanted on *recent active* rheumatic lesions, has received little consideration. This is the more surprising in that in a number of recent studies of the disease investigators have noted the frequency of the occurrence of active rheumatic endocarditis and subacute bacterial endocarditis in the same heart. We have already referred to the extensive observations of Clawson and Bell,<sup>6a</sup> Clawson, Bell and Hartzell<sup>7a</sup> and Clawson<sup>8</sup> and shall have occasion again to discuss the conclusions which they derived. Libman<sup>15</sup> recorded a case of this sort, in which both types of endocarditis existed. Leary<sup>16</sup> cited an interesting case in a boy, aged 6 years, who was run over and instantly killed. Autopsy revealed endocarditis of the mitral valve, which was found on histologic examination to be rheumatic, and his case was used to illustrate the characteristic cellular reaction of the rheumatic valvulitis. On the surface of the vegetation, however, were large colonies of gram-positive diplococci, which on culture proved to be *Streptococcus viridans*.

In a series of 10 cases of subacute bacterial endocarditis in children, Saphir and Wile<sup>17a</sup> found Aschoff bodies in every case. In discussing the relationship between the rheumatic infection and subacute bacterial endocarditis, these investigators, though accepting the specificity of the Aschoff body, were led to conclude that the "coincidental occurrence of these two conditions, though not definitely excluded, seems unlikely"<sup>17b</sup> We regard it more logical to draw the opposite conclusion.

In his discussion of their paper, Libman<sup>18</sup> said that he had "long ago noted combinations of active subacute bacterial endocarditis and recent rheumatic infections"

Although the coincidence of active rheumatic lesions with subacute bacterial endocarditis has thus attracted the attention of several observers, we have not seen expressed the view that active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of the bacteria.

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14 Boyd, W. Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p. 55

15 Libman, E. Characterization of Various Forms of Endocarditis, J. A. M. A. **80** 813 (March 24) 1923

16 Leary, T. Early Lesions of Rheumatic Endocarditis, Arch. Path. **13** 1 (Jan.) 1932

17 (a) Saphir, O., and Wile, S. A. Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, Am. Heart J. **9** 29, 1933, (b) p. 43

18 Libman, E. Am. Heart J. **9** 110, 1933

*Observations on a Series of Twenty-Six Consecutive Cases of Subacute Bacterial Endocarditis\**

Case	Age	Sex	History of Rheumatism	Rheumatic Lesions										Subacute Bacterial Endocarditis	(comment)
				Gross			Histologic								
				Adherent Pericardium	Myocardial Scars	Endocardial		Acute				Aschoff Bodies			
						Acute	Chronic	T	M	A	LA				
1	47	F	5 years ago		—	T, M	LA	+	+	+	+	+	—		
2	30	F	6 years ago	+		M	M		+				+	Perivascular myocardial scars	
3	60	M	?												
4	43	F	Chorea 34 years ago	+		M	M		+					Myocardial scars, rheumatic pericarditis	
5	11	F	3 years ago											Perivascular myocardial scars	
6	14	M	0			T	M		+					Perivascular myocardial scars	
7	42	M	0						+					Perivascular myocardial scars	
8	53	F	14 and 15 yrs ago	+			M, A		+					Perivascular myocardial scars	
9	9	F	4 years ago	+	+	T, M, A	LA	+	+	+			+		
10	37	M	6 mos ago	+	+	M	M		+	+	+		+		
11	26	M	11 years ago	+	+	M	A, LA		+	+	+		+		
12	22	F	Past few years	+	+	T	M, A	+			+	+	+	Rheumatic pericarditis	
13	58	M	40 years ago			T	M		+	+	+	+	+	Perivascular myocardial scars	
14	17	F	5 years ago	+	+	T, M	M	+	+	+	+	+	+	Perivascular myocardial scars	
15	24	F	12 years ago				M		+	+	+	+	+	Perivascular myocardial scars	
16	23	M	17, 13 and 3 years ago				M, LA		+	+				Perivascular myocardial scars	
17	35	M	22 years ago			A	M, A		+	+				Perivascular myocardial scars	
18	12	M	25 years ago, chorea 35 years ago			M, A	M		+			+	+	Perivascular myocardial scars	
19	76	F	11 years ago				T, M, A		+			+	+	Perivascular myocardial scars	
20	10	F	0			M	LA		+	+	+	+	+	Perivascular myocardial scars	
21	15	M	0				A		+	+	+	+	+	Perivascular myocardial scars	
22	25	M	12 years ago			M, A	LA		+	+				Perivascular myocardial scars	
23	23	F	? in childhood	+	+	T, M, A	M	+	+	+	+	+	+	Perivascular myocardial scars	
24	41	F	1 year ago											Perivascular myocardial scars	
25	13	F	Chorea 6 years ago			M, LA			+	+	+	+	+	Perivascular myocardial scars	
26	41	F	38 years ago				M, LA		—			+	+	Perivascular myocardial scars	

\* T indicates the tricuspid valve, M, the mitral valve, A, the aortic valve, and LA, the left auricle

Our studies have driven us to this conclusion. The evidence for it may be summarized as follows:

1. Vegetations histologically identical with those in rheumatic endocarditis and not containing bacteria are found (*a*) on the same valve as the bacterial vegetations, (*b*) on other valves on which there are no vegetations containing bacteria and (*c*) on the auricular wall.

2. Aschoff bodies in the myocardium that are taken to indicate active rheumatic disease are found in practically the same proportion of cases of subacute bacterial endocarditis as of uncomplicated rheumatic cardiac disease.

3. Types of bacterial endocarditis other than that due to nonhemolytic streptococci may be engrafted on active rheumatic vegetations. This is a cogent argument against the view that the two types of lesions are a response of different intensity to the same infective agent, unless we dispense with current views as to the histologic specificity of the rheumatic reaction.

Our observations on a series of 26 consecutive cases of subacute bacterial endocarditis are summarized in the accompanying table. In 15 of the cases, the pathologist, in his objective description of the gross valvular lesions, noted the occurrence of small, firm verrucae, which were distinct from the larger, more friable thrombotic vegetations. In sections, in each of the 26 cases there were found bacteria-free vegetations having the histologic appearance of active rheumatic verrucae. In 24 of the 26 cases, the vegetations were situated on the same valves as the bacterial vegetations. In 6 cases, they were present on other valves, namely, on the aortic valve (three times) and on the tricuspid valve (four times). In many instances, vegetations that were otherwise indistinguishable from rheumatic verrucae contained bacterial colonies in their superficial portion (figs 1 and 2). An unbroken transition could be traced between the bacteria-free rheumatic verrucae which were histologically rheumatic but contained bacteria and the larger thrombotic vegetations in which the presence of the bacteria had elicited a more or less violent cellular reaction and in which there was more or less destruction of the substance of the valve. In this we are able fully to confirm the observations of Clawson and Bell,<sup>19</sup> although our interpretation is different.

In 12 of the 26 cases (46 per cent), characteristic Aschoff bodies were found in the myocardium or at the base of the mitral valve.

The frequency of the finding of Aschoff bodies in uncomplicated rheumatic carditis is variously given. In his review, published in 1925, Sacks<sup>19</sup> cited an incidence, as given by different authors, ranging from

19. Sacks, B. The Pathology of Rheumatic Fever. A Critical Review, *Am Heart J* 1:750, 1926.

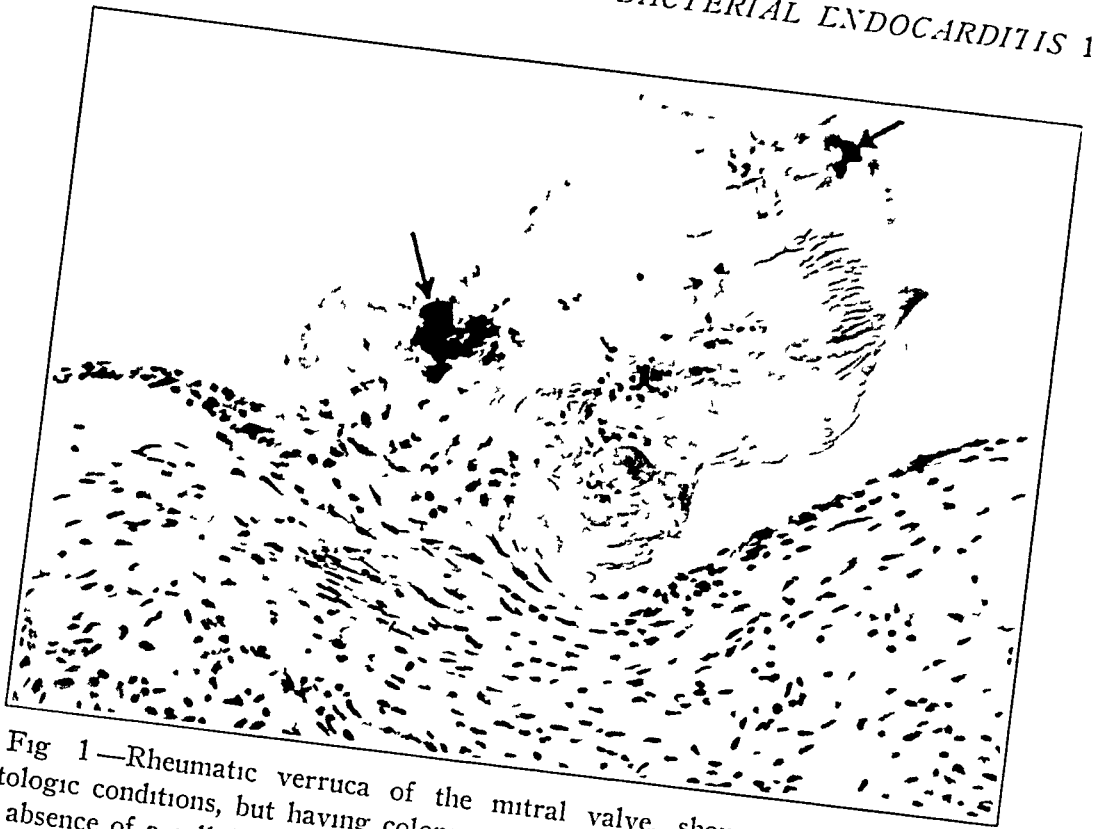


Fig 1—Rheumatic verruca of the mitral valve, showing the characteristic histologic conditions, but having colonies of bacteria (indicated by arrows) Note the absence of a cellular response

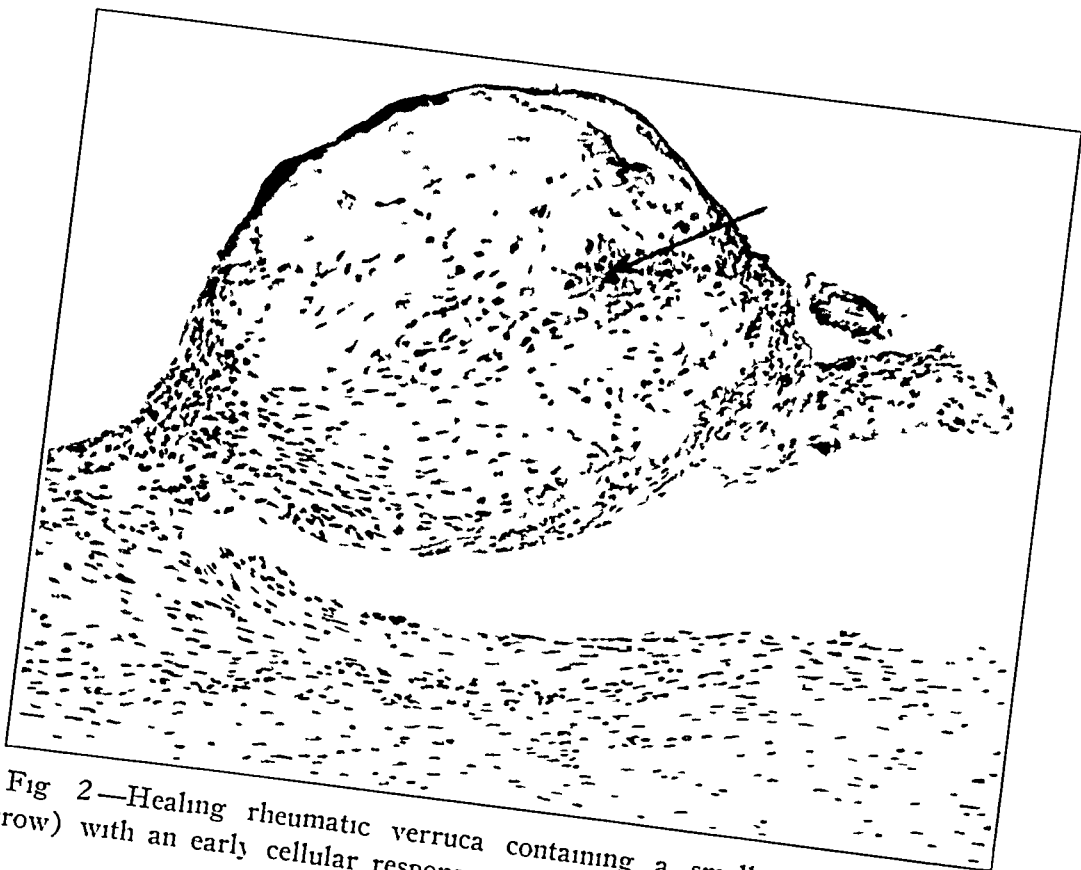


Fig 2—Healing rheumatic verruca containing a small colony of bacteria (arrow) with an early cellular response



32.1 to 87.5 per cent. In 109 cases collected from our records of four years ago, Aschoff nodules were found in 46 of 42 per cent.

The incidence is therefore practically the same in our uncomplicated cases and in those with bacterial vegetations. It agrees with curious exactness with the 45 per cent incidence reported by Clawson<sup>8</sup> in his series of 60 cases of bacterial endocarditis.

Finally, one may cite cases in which active rheumatic lesions of the valves or myocardium existed with bacterial infections of the heart valves with micro-organisms other than *Streptococcus viridans*.

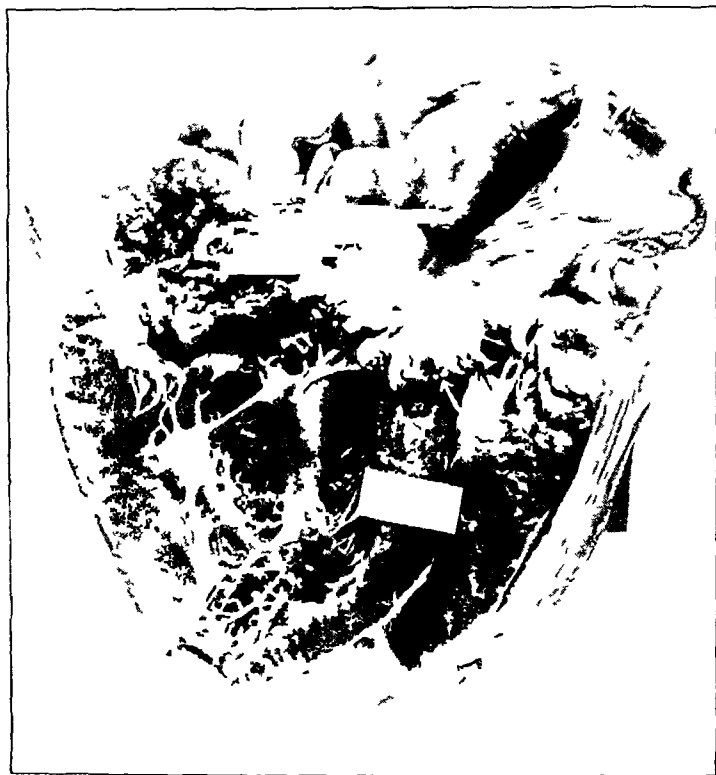


Fig. 3 (case 1)—Rheumatic and subacute bacterial endocarditis. Rheumatic verrucae on a non-aortic leaflet of the mitral valve.

The following cases will serve to illustrate the coincidence of active rheumatic carditis with subacute bacterial endocarditis.

#### REPORT OF CASES

**CASE 1**—A girl, aged 11 years, had had two attacks of rheumatic fever, the first at the age of 10 and the second three and one-half months before her admission to the hospital. Following the second attack of arthritis, precordial pain, palpitation, dyspnea and weakness developed. On examination, the heart was found to be enlarged, precordial pulsation was marked, there were apical systolic and diastolic thrills, a loud, blowing systolic apical murmur and a short, rumbling diastolic murmur. Blood culture at this time yielded no growth.

A year later, the patient was readmitted because of abdominal pain, nausea, vomiting and tenderness in the little finger. The temperature was 104 F. Only

a loud systolic murmur could be detected. The liver was enlarged and tender. Tenderness was felt over the sternum and toe. There were red blood cells in the urine. The nonhemolytic streptococcus was found on blood culture. While the patient was in the hospital, hemiplegia and other embolic phenomena developed. Death occurred six months after the diagnosis of subacute bacterial endocarditis had been established.



Fig 4 (case 1) —Subacute bacterial endocarditis of the mitral valve

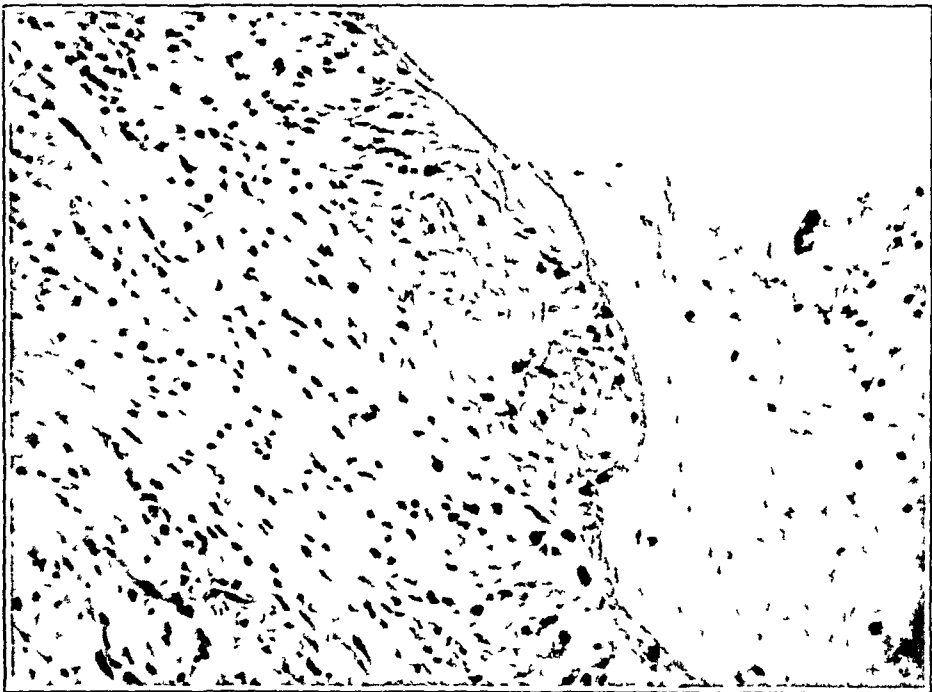


Fig 5 (case 1) —Healing rheumatic verruca of the mitral valve

The heart was enlarged and the pericardium adherent at the apex and over the great vessels, and there was 100 cc of serofibrinous fluid in the remains of the pericardial cavity. The tricuspid and pulmonic valves were normal. On the mitral valve were large, friable, yellow-gray vegetations, which extended down on the chorda tendinae for a short distance and were continued across the auricular surface of the valve to the wall of the auricle. On the posterior half of the non-aortic leaflet were a few tiny, firm gray verrucous nodules with smooth surfaces (fig 3). The aortic valves were normal.

In sections of the mitral valve, many of the excrescences had the usual appearance of bacterial vegetations, there were large colonies of gram-positive cocci on the surface, polymorphonuclears and large mononuclear cells filled with engulfed bacteria (fig 4). There were also irregular clumps of calcium. Sections through the verrucae described earlier showed a different structure. There were no bacteria to be seen, the vegetation was composed of hyaline material partly covered with endothelium, with fibroblasts growing into the base (fig 5). In the myocardium there were loose vascular scars and occasional compact avascular scars not sharply limited to the perivascular tissue. No Aschoff bodies were found in seven blocks.

This case thus illustrates the simultaneous occurrence of rheumatic and subacute bacterial vegetations on the mitral valve.

CASE 2—A stenographer, aged 22, who had had poliomyelitis in infancy, scarlet fever at 9 years and influenza at 13, noted occasional pains in the joints without fever during the four years previous to admission. Although she had no cardiac symptoms, she was told two years before entrance that she had "heart disease."

The onset of the present illness, two months before entrance, was marked by fatigue, loss of appetite and irritability. For two weeks there was edema of the ankles, and tenderness of the finger-tips was noted on several occasions.

Examination showed hemorrhage into the fundus of the right eye, a slightly enlarged heart with murmurs, secondary anemia and continued irregular fever. Blood cultures were positive for nonhemolytic streptococci. Symptoms pointed to splenic, renal and cerebral infarcts. The diagnosis of subacute bacterial endocarditis was established. Death took place about six months after the onset of the symptoms.

The heart weighed 420 Gm. There were no pericardial adhesions. The tricuspid leaflets were narrowed and thickened. On the infundibular leaflet was a narrow, yellowish-gray ridge, 7 mm in length, and somewhat granular, on the septal leaflet there was a translucent yellowish line, from 2 to 3 mm in length, and slightly elevated. On both leaflets of the mitral valve were large, friable, yellowish-gray or reddish vegetations, extended on the chordae and upward on the auricle. The auricular endocardium above the nonaortic leaflet was roughened by numerous small, opaque vegetations between which the endocardium was thick and wrinkled. The aortic cusps had large, friable vegetations extending down onto the septal endocardium. There was a mycotic aneurysm in the sinus of Valsalva behind the left posterior leaflet, when the cusps were not covered by the vegetations, they were thickened, and the edges were rolled and nodular.

Microscopically, the vegetations on the tricuspid valve were composed of somewhat hyaline material into which vertically directed fibroblasts were growing. There were no polymorphonuclears and no bacteria. The substance of the valve was thickened and scarred (fig 6).

The auricular endocardial lesions were also for the most part characteristically rheumatic, but in some places clumps of bacteria were present, and here there was intense polymorphonuclear reaction as well as many mononuclear cells. The mitral and aortic vegetations contained bacterial colonies and presented the usual picture

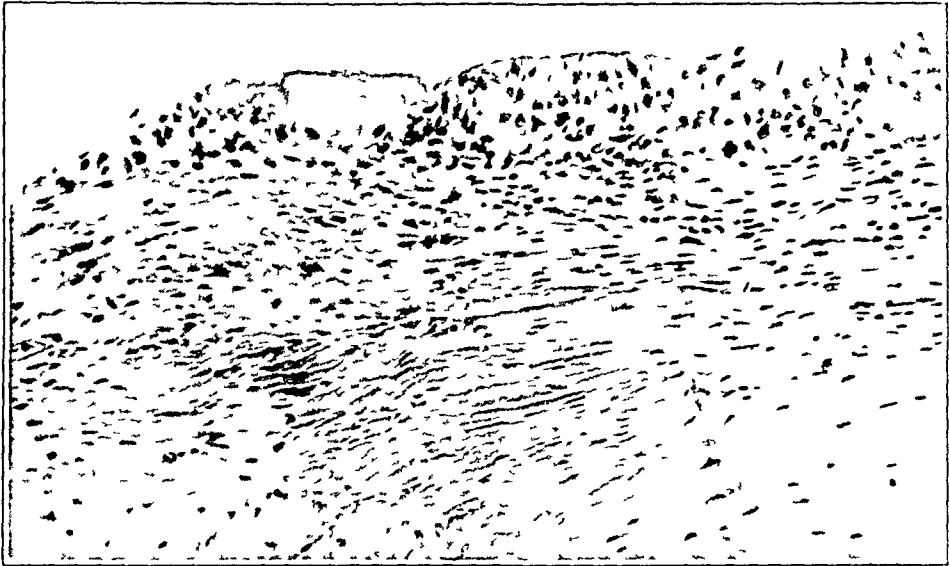


Fig 6 (case 2) —Rheumatic endocarditis of the tricuspid valve

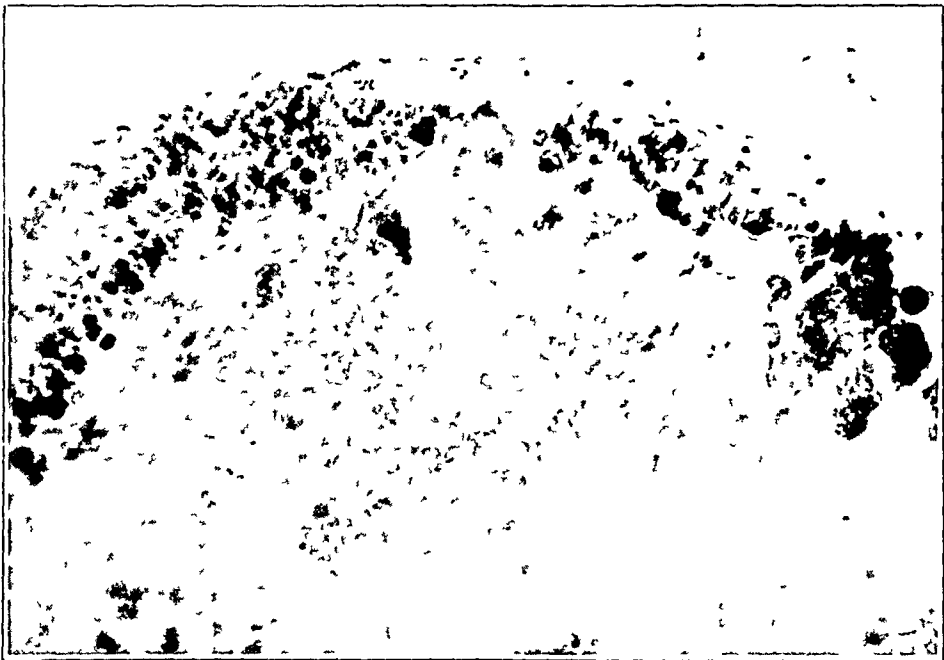


Fig 7 (case 2) —Subacute bacterial endocarditis of the mitral valve

seen in subacute bacterial lesions of these valves (fig 7). In the myocardium were numerous Aschoff nodules.

In this case, in which there was a definite history of pains in the joints, characteristic old lesions and recent rheumatic lesions were found at autopsy on the tricuspid valve and the left auricle and in the myo-

cardium The rheumatic changes on the aortic and mitral valves were obscured by the inflammatory reaction provoked by the streptococci

That bacteria other than the streptococcus may be implanted on active rheumatic valvulitis is shown by the following case

CASE 3—A boy, aged 14, at 5 years of age was discovered to have heart trouble For several years there had been occasional mild pains in the knees and hips Two weeks before entrance, an injury to the fingers of the left hand, with resulting infection, occurred Six days before entrance the patient suddenly became feverish, and several days later he had pains in the knees, hip, elbows and shoulder The heart was greatly enlarged, with a double murmur at the mitral area Hemolytic *Staphylococcus aureus* was obtained on blood culture and from the infected finger The patient died after a profound sepsis which lasted eight days

The heart weighed 380 Gm The tricuspid and pulmonic valves were normal The mitral valve was uniformly thickened, as well as the chordae tendineae There was a bulky, thrombotic vegetation on the auricular surface of the nonaortic leaflet, which extended upward on the thickened auricular endocardium The aortic cusps were also the seat of fresh thrombotic vegetations There were miliary abscesses in the myocardium Histologic study clearly showed a combination of old and recent rheumatic lesions with those attributable to the superimposed staphylococcic infection On the mitral valve were areas free from bacteria, in which the subendocardial cells showed a characteristic palisading The colonies of cocci were embedded in a compact pink-staining matrix that was being invaded by fibroblasts, and although there were many leukocytes in places, one had the impression that the vegetation was primarily rheumatic Furthermore, groups of large basophilic cells resembling Aschoff bodies were found at the base of the vegetation The myocardium contained fairly numerous typical Aschoff bodies in addition to old scars and staphylococcic abscesses

In this case we believe that the two diseases coexisted, in other words, that the patient was suffering from active rheumatic carditis when the heart became infected with *Staphylococcus aureus*

Further evidence that the two types of lesions are etiologically independent is thus afforded by case 3, in which hemolytic staphylococci were superimposed on rheumatic lesions

#### COMMENT

It seems to us that the most obvious deduction from these observations is that bacteria are implanted superficially in the hyaline or granular material of which the rheumatic vegetation is composed, in other words on an *active, unhealed* rheumatic lesion It might be argued that bacteria-free vegetations on the same valve but at a distance from the main mass of the organisms are evoked by a diffusible toxin But this assumption would not hold for cases in which bacteria-free rheumatic verrucae were situated on the tricuspid valve

The presence of Aschoff bodies may be taken as further evidence of the activity of the rheumatic process in these cases Our studies thus lead to the conclusion that it is not the old, scarred valve that is

predisposed to subsequent infection with bacteria but the valve or auricular wall which bears on its surface the fresh, unhealed verruca or plaque

The fact that in many of our cases a long interval (in one instance, forty-one years) elapsed before the patient evinced rheumatic arthritis is no argument against this conception. It is now well established that rheumatic carditis may exist in a subclinical form for many years or without any history of a pathologic condition of the joint.

It is not maintained that all cases of bacterial infection of the valves are the result of implantation on unhealed rheumatic lesions. Nor do we wish to deny the possibility that infection of the valve in cases of general sepsis may occur through the blood vessels of the valves. We have in our records several cases in which an acute interstitial valvulitis was unaccompanied by vegetations, indicating that the infection had reached the substance of the valve through the coronary circulation.

#### CONCLUSIONS

Infection of the cardiac valves with nonhemolytic streptococci in rheumatic patients is due to the implantation of the bacteria on unhealed rheumatic vegetations. The continued activity of the rheumatic disease in cases of subacute bacterial endocarditis is attested by the invariable occurrence on the valves of rheumatic verrucae which do not contain bacteria and by Aschoff bodies in the myocardium in the same percentage of cases as in uncomplicated rheumatic carditis. *Staphylococcus aureus* may also be implanted on unhealed rheumatic vegetations.

Dr. Walter W. Palmer and Dr. Allen O. Whipple permitted us to transcribe the clinical records.

# STERNAL MARROW ASPIRATED DURING LIFE

## CYTOLOGY IN HEALTH AND IN DISEASE

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Although the importance of studies of the bone marrow in hematologic disorders is well known, few examinations of the bone marrow have been made during life. Simultaneous examinations of the peripheral blood and the bone marrow have been made feasible by Arinkin's<sup>1</sup> simple method of obtaining bone marrow by sternal puncture. Using a similar technic, we have studied the marrow of twenty-eight healthy men and twenty-six patients.

Ghedini<sup>2</sup> was apparently the first to describe a technic for taking a specimen of bone marrow for biopsy. His method of trephining the tibia was little used. Seyfarth<sup>3</sup> also used a method of trephining, but suggested that the sternum was more suitable for routine studies than the tibia. Peabody<sup>4</sup> studied the bone marrow in pernicious anemia, using Ghedini's technic for the removal of marrow. His work has done much to establish the procedure as a diagnostic aid and as a reliable method of studying the function of bone marrow.

Arinkin<sup>1</sup> introduced a simple technic for obtaining bone marrow from the manubrium sterni by aspiration through a spinal puncture needle. Since then investigations by Arinkin<sup>5</sup> and by other European

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From the Department of Medicine, University of Oregon Medical School.

1 Arinkin, M I. Methodology of Examining Bone Marrow in Live Patients with Hematopoietic Diseases, *Vestnik khir* **10** 57, 1927.

2 Ghedini, G. Per la patogenesi e per la diagnosi delle malattie del sangue e degli organi emopoietici, *punctura esplorativa del midollo osseo*, *Clin med ital* **47** 724, 1908, *Neue Beitrage zur Diagnostik der Krankheiten der hamatopoetischen Organe mittels Probepunktion des Knochenmarks*, *Wien klin Wchnschr* **23** 1840, 1910, *Die Technik der Knochenmarkspunktion*, *ibid* **24** 284, 1911, cited by Peabody.<sup>4</sup>

3 Seyfarth, C. Die Sternumtrepanation, eine einfache Methode zur diagnostischen Entnahme von Knochenmark bei Lebenden, *Deutsche med Wchnschr* **49** 180 (Feb 9) 1923.

4 Peabody, F W. The Pathology of the Bone Marrow in Pernicious Anemia, *Am J Path* **3** 179 (May) 1927.

5 Arinkin, M I. (a) Morphologic Changes in Composition of Bone Marrow Obtained from the Thoracic Cavity by Puncture in Cases of Pernicious Anemia During Remissions, *Klin med* **7** 135, 1929, (b) Die intravitale Untersuchungsmethodik des Knochenmarks, *Folia haemat* **38** 233 (June) 1929.

workers<sup>6</sup> have shown that this is a practical and useful clinical procedure. The excellent description and analysis of this technic by Tuschinsky and Kotlarenko<sup>6a</sup> is worthy of special mention. The only American publication is a short report by Holmes and Broun.<sup>7</sup> Few studies on normal persons have been included in the published reports. Broun's<sup>8</sup> excellent preparations, seen while visiting his laboratory (E. E. O.), and the lack of normal standards led to our selection of this problem for study.

#### TECHNIC OF STERNAL PUNCTURE

The technic of sternal puncture that we found to be most satisfactory is as follows. With the patient lying on his back, with his chest elevated by a pillow beneath his shoulders, the region of the sternomanubrial junction is prepared with iodine and alcohol. Using aseptic technic, the sternomanubrial junction is located as a distinct ridge opposite the sternal cartilages of the second ribs, and the skin, the subcutaneous tissues and the periosteum of the region are infiltrated with procaine hydrochloride. Using an 18 gage spinal puncture needle, from 3 to 4 cm in length, the sternomanubrial junction is entered in the midline at an angle of about 60 degrees to the surface of the chest. Then the needle is depressed to an angle of about 30 degrees and is forced into the marrow cavity of the body of the sternum, care being taken not to exceed a depth of 1.5 cm. If much resistance is encountered, the needle is rotated while pressure is maintained to facilitate penetration. The stylet is then removed, and, using a 2 cc Luer syringe, 1 or 2 cc of marrow is aspirated. If no marrow appears after strong aspiration, the stylet is replaced, the needle is inserted a little deeper and aspiration is done. We then remove the syringe from the needle and transfer the aspirated material, which looks like blood, into a 4 by ½ inch (10.16 by 1.27 cm) test tube containing from 2 to 4 mg of powdered potassium oxalate shaking well to insure mixing. The stylet is then replaced, the needle is withdrawn and the puncture wound is sealed with collodion.

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6 (a) Pokrovsky, V. I. Das Verhältnis der Substantia reticulo-filamentosa im Knochenmark und im peripheren Blute bei verschiedenen Erkrankungen innerer Organe, *Folia haemat* **39** 265 (Dec.) 1929. (b) Arjeff, M. J. Zur Methodik der diagnostischen Punktion des Brustbeines, *ibid* **45** 55 (Aug.) 1931. (c) Barta, I. Die Bedeutung der Sternalpunktion bei Anämien und über die Beeinflussung des Knochenmarkes durch Leberbehandlung, *Deutsches Arch. f. klin. Med.* **171** 565 (Sept. 21) 1931. (d) Tuschinsky, M. D., and Kotlarenko, B. N. Ueber Knochenmarkveränderungen bei Flecktyphus mit Bemerkungen zur Methodik der diagnostischen Punktion des Sternalmarks und der Anfertigung von Knochenmarkpunktatpräparaten, *Folia haemat* **46** 235 (Feb.) 1932. (e) Tempka, T., and Braun, B. Das morphologische Verhalten des Sternumpunktates in verschiedenen Stadien der perniziösen Anämie und seine Wandlungen unter dem Einflusse der Therapie, *ibid* **48** 355 (Nov.) 1932.

7 Holmes, W. F., and Broun, G. O. Clinical Study of Bone Marrow by the Method of Sternal Puncture, *Proc. Soc. Exper. Biol. & Med.* **30** 1306 (June) 1933.

8 Broun, G. O. Personal communication to the author.



The oxalated marrow can be used for any type of hematologic examination which can be done on oxalated blood<sup>9</sup>

This technic was developed by an analysis of each step in the procedure, as indicated in the following paragraphs

Broun<sup>8</sup> felt that the procedure caused so little pain that an anesthetic was hardly necessary. However, by the use of procaine hydrochloride all sensation except that of pressure during the insertion of the needle and a peculiar drawing pain during aspiration of the marrow is eliminated. The pain is slight and entirely localized if 2 cc or less is slowly aspirated. Rapid withdrawal of larger amounts may cause considerable discomfort, often referred to the lower end of the sternum or to the upper extremities.

A full length spinal puncture needle was used by Arinkin<sup>5b</sup> and others, but we found that a shorter needle, similar to that suggested by Tuschinsky and Kotlarenko,<sup>6a</sup> is more convenient and less likely to break. Since Arjeff<sup>6b</sup> found the anterior lamina of the sternum thicker than the posterior lamina, he devised a special needle with an adjustable guard for limiting the depth of penetration. We found that by inserting the needle at an angle and by bracing the fingers against the chest the possibility of going entirely through the sternum is practically eliminated.

Various investigators have chosen different sites for the puncture. Arinkin<sup>5b</sup> punctured the anterior lamina of the manubrium directly. Tuschinsky and Kotlarenko<sup>6a</sup> penetrated the body of the sternum slightly to the right of the midline at the level of the third rib, with the needle at an angle of 45 degrees. Broun<sup>8</sup> suggested entering the sternomanubrial junction, and we have found this to be the most satisfactory procedure because less pressure is required to enter the marrow cavity. However, if the sternomanubrial junction is not readily found, the needle may be forced through the anterior lamina of the body of the sternum by the application of more pressure.

Several authors have reported inability to obtain bone marrow owing to a marked thickness of the anterior lamina of the bone or to lack of depth of the bone marrow cavity. Arinkin<sup>5b</sup> noted that persons with wide sternal bones are likely to have small marrow cavities. We have had five failures in sixty-two attempts to obtain biopsy specimens. The failures occurred in our early attempts, and may be ascribed to inexperience and timidity. We found that one gains confidence by practice on cadavers.

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9 (a) Osgood, E. E., Haskins, H. D., and Trotman, F. E. A Uniform System of Hematologic Methods for Use with Oxalated Venous Blood, *J. Lab. & Clin. Med.* **16** 476 (Feb.) 1931. (b) Osgood, E. E., and Haskins, H. D. A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Company, 1931, p. 344.

Most authors did not mention the use of an anticoagulant but made direct smears immediately. Following Broun's<sup>9</sup> suggestion, we at first aspirated the bone marrow directly into a sterile 2.5 per cent solution of sodium citrate. When unsatisfactory preparations were secured by this technic, we tried centrifugation and also mixing with the patient's blood serum, as suggested by Isaacs.<sup>10</sup> Because of our previous experience with oxalated venous blood,<sup>9</sup> we tried powdered potassium oxalate as an anticoagulant for the bone marrow and found it to give the most satisfactory preparations. This method is simpler and more convenient than the others tried, because it is not necessary to use the marrow immediately, to centrifugate it or to obtain the patient's serum. The preparation also permits hematologic studies other than examination of stained smears.

#### RESULTS

Differential peroxidase and reticulocyte counts were made on the oxalated marrow and on oxalated venous blood taken at about the same time. Using the same technic as for blood, thin smears were made on glass slides and stained with Wright's stain, using a buffer phosphate solution with a  $p_H$  of 6.4. Five hundred nucleated cells were counted, including normoblasts, megaloblasts, megalokaryocytes and degenerating cells, and the percentages were calculated. The details of cellular morphology in the preparations of bone marrow were as clearly defined as in the best preparations obtained from blood (figs. 1, 2 and 3).

Peroxidase stains were prepared by a modified Washburn technic.<sup>11</sup> From 200 to 500 cells were counted.

The reticulocytes were stained with 1 per cent brilliant cresyl blue in an 0.85 per cent solution of sodium chloride,<sup>12</sup> thin smears were made and the reticulocytes in 1,000 red cells were counted.

*Cell Counts in Bone Marrow and Blood of Normal Subjects*—The results of our studies of the venous blood and sternal marrow of twenty-eight healthy male medical students are given in table 1. It is noteworthy that the range of variation in the differential cell counts of the marrow was little greater than that of the blood. As one would expect, the segmented granulocytes were less numerous and the staff cells were much more numerous in the marrow than were the corresponding cells in the blood. Some metamyelocytes and a few of each of the less mature granulocytes were found in the marrow, while similar cells were absent from the blood. The lymphocytes were definitely less

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<sup>10</sup> Isaacs, R. Alteration of Tissue Cells in the Blood Stream, *Science* **68**: 547 (Nov. 30) 1928.

<sup>11</sup> Osgood and Haskins.<sup>9b</sup>

<sup>12</sup> Osgood, E. E., and Wilhelm, Mable M. Reticulocytes, *J. Lab. & Clin. Med.* **19**: 1129 (July) 1934.

TABLE 1—Differential Counts on Stenal Marrow and Venous Blood of Twenty-Eight Normal Persons<sup>4</sup>

Case Number	Red Blood Cells, Millions	Hemoglobin, Gm	White Blood Cells	Segmented Neutrophils	Segmented Eosinophils	Segmented Basophils	Neutrophil Staff Cells	Eosinophil Staff Cells	Basophil Staff Cells	Neutrophil Metamyelocytes	Eosinophil Metamyelocytes	Neutrophil Myelocytes	Promyelocytes, Type I	Promyelocytes, Type II	Myeloblasts	Lymphocytes	Monocytes	Normoblasts	Megaloblasts	Disintegrating Cells	Reticulocyte	Myeloid Erythroblast Ratio
1	5.73	17.14	9,670	15.1 44.0†	3.0		22.6 4.0	0.8		6.8	0.8	0.8	2.4	3.0	0.1	11.0 43.0	0.6 2.0	13.0	1.1	21.0	1.9 2.4	3.68 1
2	4.91	15.69	7,800	13.0 58.0	0.6 2.0	0.2 1.0	3.8 6.0	1.0		6.8	0.4	0.1	2.6	2.2	0.1	12.6 33.0	0.8	8.6	0.6	18.1	1.2 1.2	6.31 1
3	5.29	14.46	9,350	14.0 53.0	0.4		24.2	1.0		7.0	1.2	1.0	3.0	1.0	0.8	12.4 41.0	1.0 6.0	14.8	1.0	16.8	2.1 3.6	3.68 1
4	5.01	15.97	7,000	9.2 45.0	0.4 2.0		21.0 5.0	1.0		9.0	0.2	1.4	2.0	2.0	0.2	9.8 46.0	1.6 2.0	18.2	1.6	20.6	2.1 2.2	2.49 1
5	4.41	13.93	11,500	10.8 74.0	0.6 3.0		30.2	0.2		9.8	0.1	0.6	3.0	3.8	0.4	8.8 17.0	1.6 6.0	11.8	2.0	15.4	1.3 2.0	4.35 1
6	4.40	13.52	9,750	7.1 43.0	1.0		28.8			7.6	1.0	1.0	1.6	1.2		10.4 47.0	1.2 9.0	12.2		27.2	1.8 1.6	3.98 1
7	5.45	18.52	8,300	9.0 59.0	1.0 2.0	1.0	20.2	1.4		8.4	1.2	0.6	2.2	2.2	1.2	12.4 32.0	1.8 4.0	10.8	1.4	20.2	2.3 1.6	4.37 1
8	4.77	12.70	9,500	13.6 55.0		0.2	21.1	0.8		6.2	0.2	0.1	1.0	1.2	0.2	9.6 45.0	1.2	20.0	1.4	22.6	2.4 2.4	2.10 1
9	5.00	15.18	6,700	11.6 45.0	1.0		21.0	1.0		8.0	2.0	1.1	3.1	2.2	0.8	4.8 51.0	1.2 4.0	12.8	3.0	25.2	1.8 1.0	3.32 1
10	5.75	18.52	9,700	13.8 52.0	0.4	0.2	23.4			8.0	0.4	1.4	0.8	0.8	0.6	10.0 47.0	1.6 1.0	13.0	1.6	24.4	1.7 1.8	3.41 1
11	4.69	12.86	9,050	17.2 38.0	0.6 2.0	0.2	16.8	0.6		5.2	0.4	0.4	0.6	1.6		11.2 58.0	1.2 2.0	18.0	1.6	23.8	1.8 1.4	2.22 1
12	4.82	13.31	6,300	15.2 58.0	0.8 3.0		20.2	1.4		7.8	1.0	0.8	0.8	1.6		3.6 34.0	5.0	16.0	1.8	31.8	1.7 0.6	2.79 1
13	4.53	13.91	12,250	22.4 65.0	0.8 2.0	1.0	15.8 7.0	0.2		8.8		0.1	0.4	1.0		5.2 21.0	4.0	16.6	0.8	27.4	1.1	2.86 1

14	5.27	16.26	8,950	8.6	0.6	29.8	1.0	0.2	8.8	0.6	0.4	2.2	1.4	0.4	8.4	2.2	13.6	3.8	18.0	2.2	3.10	1
15	5.88	15.80	8,200	25.2	1.0	0.2	16.2	0.4	1.8				0.2		29.0	4.0	6.6	0.4	31.2	1.6	0.25	1
16	5.14	15.69	6,250	10.2			16.0	0.6	0.2	8.0	0.8	1.0	1.6	0.4	14.0	2.0	11.2	1.6	29.4	1.7	3.15	1
17	5.07	14.15	8,850	13.8	0.4		33.0	1.4	7.8	1.0	0.8	1.0	1.0	0.4	9.8	3.6	6.6	1.4	17.8	1.5	7.77	1
18	4.80	16.55	13,650	14.2	0.8	0.2	26.4	1.4	9.8	0.2	0.6	0.4	1.4		12.0	2.4	5.4	1.4	23.8	2.0	8.11	1
19	4.79	14.04	7,450	10.4			22.0	0.6	7.4	0.4	0.4	0.2	0.2	0.6	10.6	0.4	17.2	4.2	24.8	1.9	2.00	1
20	5.68	19.37	8,700	13.6	0.6	0.2	25.2	1.4	8.0	1.6	2.6	4.0	1.8	0.8	11.4	1.4	7.1	0.8	11.4	2.2	7.11	1
21	5.14	16.77	7,100	7.4	1.0		28.4	0.6	6.2	0.6	1.2	1.8	0.6	0.4	11.6	3.8	1.4	2.2	19.0	2.1	1.12	1
22	4.96	16.94	6,650	12.0	0.6	0.2	20.6	0.8	8.0	0.8	0.6	1.0	1.4	0.2	13.0	2.2	12.4	3.0	22.8	1.9	1.00	1
23	5.20	17.47	7,900	11.8	0.2		27.6	1.6	9.6	1.2	0.6	2.0	1.2	0.6	8.6	3.8	10.6	2.4	15.6	3.2	1.55	1
24	5.18	16.55	9,750	12.2	0.2		25.8	0.6	6.8	0.2	0.2	1.2	1.6		11.6	1.2	7.6	1.6	21.4	2.1	3.12	1
25	5.12	14.25	5,950	18.4	1.0	0.2	27.4	1.2	6.2	0.6	1.0	2.0	1.8	0.8	10.4	3.0	6.8	0.6	15.6	1.8	9.21	1
26	5.19	16.98	9,150	14.2	0.4		27.4	1.2	5.4	0.2	1.6	1.6	1.0	0.8	9.6	3.4	11.1	2.8	15.4	1.3	3.51	1
27	5.70	17.94	7,750	14.2	0.4	0.2	26.6	1.2	7.6	0.4	1.6	2.8	1.4	0.8	9.4	2.8	15.4	1.4	12.8	2.5	1.10	1
28	5.00	15.83	7,750	13.8	0.8	0.2	38.6	0.6	6.1	0.2	0.8	1.4	1.0	1.0	16.0	3.4	13.2	2.0	19.8	1.8	2.91	1
Average	5.09	15.72	8,600	13.3	0.4	0.1	24.1	0.8	7.4	0.6	0.8	1.7	1.5	0.4	10.6	2.1	12.4	1.7	20.8	1.9	1.61	1
Maximum	5.88	19.37	13,650	25.2	1.0	0.2	33.0	1.6	9.8	2.0	2.6	4.0	3.8	1.2	16.0	4.2	20.0	4.2	31.8	3.2	8.29	1
Minimum	4.82	12.70	5,950	7.4	0.0	0.0	15.8	0.0	1.8	0.0	0.0	0.0	0.0	0.0	4.8	0.0	5.4	0.0	12.8	1.2	2.00	1

\* The figures for each type of cell are given in per cent. The percentages of basophil myelocytes, Turk cells, plasma cells, mitotic cells and megakaryocytes were so small that they are omitted.  
† The reticulocytes are in per cent of red cells.  
‡ The figures in bold face represent differential counts on blood taken at the time of the bone marrow biopsy.

numerous and the monocytes slightly less numerous in the marrow than in the blood. Degenerating cells, which were included in the differential count, were abundant in the bone marrow and were seldom found in the blood. There was little difference in the reticulocyte count in the bone marrow and in the blood.

With the exception of the mature erythrocyte, the predominant cell in the bone marrow (fig 1) was the neutrophil staff cell. Segmented neutrophils and normoblasts were next in frequency. A few megaloblasts were present. Turk cells, Marschalko plasma cells and megalokaryocytes were seldom encountered in making the differential count, but were demonstrable, by a careful survey, in almost every preparation. Mitoses in nucleated red cells were occasionally seen. The cellular morphology



Fig 1—Bone marrow of a normal healthy man

was so clearly defined that it was seldom necessary to designate a cell as unclassified. The monocytes and all the cells of the myeloid series, except myeloblasts, gave a positive peroxidase reaction. The ratio of the total myeloid cells to the total nucleated red cells varied from 8.29:1 to 200:1 and averaged 3.61:1.

Table 2 summarizes for comparison, all the differential counts available on normal bone marrow obtained by sternal puncture. The apparent discrepancies may be explained by the different criteria for classification of the cells and by the fact that our differential counts were the only ones to include disintegrating cells. It is noteworthy that all who have reported reticulocyte counts found approximately equal percentages in bone marrow and in blood. Comparison of the myeloid-erythroblast ratios shows them to agree.

*Cell Count in Bone Marrow and Blood of Persons with Pathologic Conditions*—The results of studies of the marrow and blood in twenty-six cases representing fifteen different disorders of the blood and blood-forming organs are summarized in table 3

## REPORT OF CASES

CASE 1—A man, aged 28, was selected as a normal subject, but study of the marrow revealed a definite increase in the number of eosinophil cells of all types. Eosinophilia was also found in the blood, for which no cause was discovered.

TABLE 2—Summary of Reported Differential Cell Counts on Sternal Marrow from Normal Persons

	Arinkin	Holmes and Brown	Tempka and Braun*	Young and Osgood
	Range	Average	Range	Range
Number of cases	?	7	3	23
Segmented neutrophils	41.0 to 55.0	17.4	16.2 to 20.3	7.4 to 27.2
Segmented eosinophils	0.6 to 4.0	1.0	0.7 to 2.5	0.0 to 1.0
Segmented basophils	0.0 to 0.7	0.3	0.2 to 0.3	0.0 to 0.2
Neutrophil staff cells†		14.0	17.0 to 22.5	15.8 to 35.0
Eosinophil staff cells			0.5 to 1.0	0.0 to 1.6
Basophil staff cells			0.0 to 0.2	0.0 to 0.6
Neutrophil metamyelocytes	1.4 to 5.4	6.7	14.3 to 16.2	1.8 to 9.8
Eosinophil metamyelocytes	0.3 to 1.0		0.3 to 3.7	0.0 to 2.0
Basophil metamyelocytes			0.0 to 0.2	
Neutrophil myelocytes	4.5 to 8.6	7.0	12.7 to 13.3	0.0 to 2.6
Eosinophil myelocytes	0.3 to 1.0		1.5 to 2.7	0.0 to 0.4
Basophil myelocytes			0.0 to 0.3	
Promyelocytes, type I				0.0 to 4.0
Promyelocytes, type II	1.0 to 2.8		3.7 to 6.8	0.0 to 3.8
Myeloblasts (stem cell)	1.0 to 2.4	2.4	4.6 to 7.0	0.0 to 1.2
Lymphocytes	7.3 to 16.5	24.9	2.6 to 3.3	4.8 to 16.0
Monocytes (reticulo endothelial)	2.1 to 9.3	9.0	0.5 to 0.8	0.0 to 4.2
Normoblasts	5.7 to 16.0	6.9	13.3 to 16.6	5.4 to 20.0
Megaloblasts	0.8 to 2.9	5.2		0.0 to 4.2
Megalokaryocytes	0.6 to 6.1		2.2 to 4.0	0.0 to 0.2
Plasma cells (Türk cells included)	0.3 to 0.9		0.3 to 1.6	0.0 to 1.0
Disintegrating cells				12.8 to 31.8
Reticulocytes‡	0.8 to 1.4		0.8	1.2 to 5.2
Myeloid erythroblast ratio§	7.70 to 41.7	4.86	5.83 to 5.39	8.29 to 20.0

\* Nucleated erythrocytes were not included in the differential count. These figures are calculated from Tempka and Braun's data.

† Arinkin did not differentiate staff cells from the segmented cells. The percentage of reticulocytes was reported by Pokrovsky.<sup>6a</sup>

‡ The figures for reticulocytes are in per cent of red cells.

§ The ratio was calculated from the authors' data.

CASE 2—A youth, aged 16, had neutrophilic leukocytosis, an increase in the number of staff cells caused by bronchopneumonia and empyema due to *Streptococcus haemolyticus*. The marrow showed an increase in the number of immature neutrophils of all types, promyelocytes, myeloblasts and plasma cells.

CASE 3—A girl, aged 17, had unexplained leukopenia (count, from 1,850 to 6,500 cells) of at least six months' duration. The diagnosis of aleukemic myelosis was being considered, but the only variation from the normal in the bone marrow was a decrease in the number of segmented neutrophils. The patient remained under observation and seemed to have physiologic leukopenia of the type described by Roberts and Kracke.<sup>13</sup>

13 Roberts, S. R. and Kracke, R. R. Agranulocytosis. Its Classification, Cases and Comments Illustrating the Granulopenic Trend from 8,000 Blood Counts in the South. *Ann Int Med* 5:40 (July) 1931.

TABLE 3—Differential Count on Sternal Marrow and Venous Blood of Twenty-Six Patients with Pathologic Conditions\*

Case Number	Diagnosis	Red Blood Cells, Millions	Hemoglobin, Gm	White Blood Cells	Segmented Neutrophils	Segmented Eosinophils	Segmented Basophils	Neutrophil Staff Cells	Eosinophil Staff Cells	Basophil Staff Cells	Neutrophil Metamyelocytes	Eosinophil Metamyelocytes	Neutrophil Myelocytes	Promyelocytes, Type I	Promyelocytes, Type II	Myeloblasts	Lymphocytes	Monocytes	Normoblasts	Megaloblasts	Disintegrating Cells	Retenulocytes	Myeloid Erythroblast Ratio
1	Leukopenia	4.79	14.46	8,250	26.4† 54.0	4.8 15.0	0.4 3.0	17.0	2.0		6.4	1.4	2.8	0.6	3.8	0.6	5.4 25.0	3.0	7.6	2.4	17.2	4.8 1.2	0.08 1
2	Streptococcal pneumonia	5.16	14.25	27,000	12.0 62.0	0.4		34.8 24.0	1.0		12.0	1.0	2.0	4.4	5.0	1.4	6.8 9.0	0.2 5.0	3.0	2.2	9.1	0.9	14.20 1
3	Leukopenia	4.77	11.35	4,650	2.4 61.0	0.8		22.2 4.0	0.6		3.4	0.2		1.2	3.8	0.2	5.8 30.0	0.2 5.0	23.6	3.4	32.8	1.2 1.6	1.29 1
4	Aplastic anemia	1.43	3.80	1,350	0.0 24.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1 0.1	
5	Carcinoma of stomach	2.67	3.35	7,300	7.0 60.0	0.2	1.0	19.8	0.2		7.0		0.8	1.0	0.4	0.4	16.0 30.0	0.2 2.0	30.4	3.4	13.2 7.0	3.9	1.07 1
6	Uterine fibroids	2.90	4.46	3,550	17.8 52.0	2.0		31.0 3.0	0.6		8.0		1.6	1.2	1.0	0.4	7.2 40.0	0.6 3.0	21.0	1.8	7.4	4.6 2.3	2.70 1
7	Congenital syphilis	1.63	4.10	2,800	1.4 36.0			6.4 3.0			2.6		0.2	0.8	2.2		10.8 60.0	1.0 1.0	50.4 1.0	5.0 1.0	19.6 1.0	1.4 3.0	0.24 1
8	Tertiary syphilis	3.29	6.98	4,850	16.0 52.0	0.6	0.4	17.2	0.6		3.8	0.4	0.1	0.8	1.2	0.6	20.6 43.0	2.4 5.0	12.0	1.6	18.2	0.9 2.4	3.09 1
9	Still's disease	3.64	8.82	6,070	21.8 55.0	0.8 1.0		31.6	1.8		5.8	0.4	3.0		8.2		7.8 31.0		9.4	2.4	7.4	1.9	6.05 1
10	Nephritis	3.37	9.08	9,570	8.6 52.0	0.2		41.2 10.0	0.8		9.8	0.6	1.4	0.8	0.8	1.4	6.6 22.0	1.0 6.0	9.0	0.4	16.2 6.0	5.7	6.98 1
11	Nephritis	2.01	5.44	15,500	8.2 79.0			18.4	0.2		6.0		0.6	0.8	1.1		6.2 17.0	0.4	37.4	2.2	16.8 3.0	15.9 8.0	0.90 1
12	Lead poisoning	4.15	11.19	13,000	8.6 59.0	0.4 2.0		24.0 5.0	1.0		7.6	1.2	1.8	0.8	1.4	0.8	7.0 32.0	2.2 2.0	27.6	4.4	9.8	11.1 7.6	1.25 1
13	Hemolytic icterus	4.98	14.57	9,650	7.0 50.0	0.4 3.0	1.0	18.2	0.2		6.6	0.8	1.4	4.2	2.8	1.2	5.4 46.0	0.2	26.2	10.6	13.2	8.7 8.0	1.17 1

14	Banti's disease	363	9,580	3,550	42	0.2	1.2	0.2	4.6	7.8	0.6	1.0	2.0	28.8	14.2	9.6	105.1
15	Pernicious anemia	120	5,675	3,070	4.6	1.6	6.4	0.5	1.1	2.1	1.2	9.2	20	24.2	16.8	30.0	207.1
		263	8,822	6,170	15.1	0.2	10.6		0.1	0.8	0.2	15.6	0.6	24.2	2.0	27.8	2.4
					61.0		3.0					29.0	4.0			1.0	113.1
16	Pernicious anemia	189	5,665	3,530	15.6	1.4	6.6	0.1	1.1	7.2	0.6	6.2		10.6	6.4	41.8	213.1
		210	6,114	3,760	11.0	0.6	17.2		0.6	1.1	1.0	3.2	1.0	29.6	6.0	21.0	163.1
					70.0		1.0					28.0	1.0			7.6	7.6
17	Pernicious anemia	153	5,770	3,150	8.0	1.2	8.4	1.0	0.5	0.8	1.6	11.0	0.2	17.6	17.4	21.0	0.75.1
					62.0	1.0						33.0	4.0			1.1	1.1
18	Pernicious anemia	169	7,065	2,800	13.8	0.6	11.1	1.2	0.1	1.0	2.0	17.6	0.6	12.6	10.8	21.0	2.3
					37.0	1.0	2.0					57.0	3.0				1.63.1
19	Hodgkin's disease	421	12,200	8,900	23.8	1.2	21.1	0.6	0.8	0.1	0.2	17.8	2.2	5.4	1.2	17.0	824.1
					71.0							24.0	5.0				1.2
20	Hodgkin's disease	421	11,041	10,950	22.0	0.8	35.2	1.2	1.6	3.0	3.6	5.1	1.6	3.8	0.8	10.2	3.7
					92.0							5.0	2.0			1.0	1680.1
21	Myelogenous leukemia	302	8,622	260,000	7.2	1.4	28.0	2.0	6.8	13.6	8.0	1.6	0.2	2.0	2.0	5.2	35.10.1
					23.0	2.0	28.0	4.0	1.0	2.0	2.0					3.0	3.0
					4.6	5.0	23.6	1.0	3.0	6.6	2.0	1.6	0.2	1.8	0.4	10.0	34.70.1
					23.0	5.0	30.0		16.0	9.0		2.0					
22	Myelogenous leukemia	375	10,211	216,000	10.2	0.2	25.0	0.2	1.2	3.0	1.6	6.0	0.8	18.8	1.4	20.8	237.1
					47.0		3.0					37.0	5.0			6.0	
23	Myelogenous leukemia	390	10,133	7,900	13.1	0.2	26.2	0.1	1.2	2.0	1.4	5.0	1.6	20.2	5.0	15.2	2.09.1
					70.0	2.0						19.0	8.0			1.2	1.2
					14.0	0.2	10.6	0.8	0.1	1.8	2.8	4.0	1.2	4.4	0.4	29.0	12.25.1
					54.0		3.0			11.0	24.0					6.0	
24	Monocytic leukemia	398	10,792	25,250	0.0		0.4					7.4	42.0†			50.0	0.3
					0.8		1.2					42.6	27.6	0.2		43.4	
25	Xanthomatosis	401	11,222	5,050	0.0		7.4		5.6	0.6	8.0	42.6	1.0	6.4	3.8	19.2	2.08.1
					0.0		48.0			1.0		50.0					
26	Multiple myeloma§	344	8,792	9,500	35.0	0.4	14.0		0.4	1.8	1.8	19.6	0.2	4.2	2.6	13.5	1.2
					54.0	3.0	2.0					32.0	7.0				812.1

\* The figures for each type of cells are given in per cent. The percentages of basophil myelocytes, Turk cells, plasma cells, mitotic cells and megakaryocytes were so small that they are omitted.

† The figures in bold face in the first line represent deviations from the normal, and those in bold face in the second line represent differential counts on specimens of blood taken at the time the biopsy on the bone marrow was made.

‡ Monocytes, 42 per cent, include mature monocytes, 0.2 per cent, promonocytes, 10.0 per cent, and monoblasts, 31.8 per cent.

§ Two and six tenths per cent plasma cells were present.



CASE 4—A man, aged 62, had aplastic anemia following the administration of neoarsphenamine. Practically no nucleated cells were found in the marrow, and reticulocytes were very scarce.

CASE 5—A woman, aged 40, had anemia due to chronic hemorrhage secondary to advanced carcinoma of the stomach. The only deviations from the normal count in the marrow were a marked increase in the number of normoblasts and microcytosis, hypochromia and poikilocytosis similar to those observed in the blood.

CASE 6—A woman, aged 39, had chronic hemorrhagic anemia due to uterine bleeding secondary to fibromyomas. The marrow showed an increase in the number of normoblasts similar to the increase in case 5.

CASE 7—A girl, aged 5 years, had severe anemia with leukopenia. Clinically, aplastic anemia, aleukemic myelosis and anemia of congenital syphilis were considered. The marrow showed a striking increase in normoblasts, a moderate increase in the number of megaloblasts and a decrease in the number of segmented granulocytes and staff cells. This picture was incompatible with a diagnosis of aplastic anemia or aleukemic myelosis. A report of 4 plus Kolmer and Kahn reactions of the child and of her mother confirmed the diagnosis of congenital syphilis. The patient made a rapid recovery following transfusions of blood and antisyphilitic therapy.

CASE 8—A man, aged 50, with mild anemia, tertiary syphilis and hypertension, had been treated for pernicious anemia in a veterans' hospital. The marrow was essentially normal, and the blood findings and the amount of free hydrochloric acid in the gastric contents excluded a diagnosis of pernicious anemia.

CASE 9—A man, aged 19, had mild anemia. A clinical diagnosis of Still's disease was made. The only noteworthy change in the marrow was an increase in the number of segmented neutrophils and staff cells.

CASE 10—A boy, aged 5 years, had acute glomerular nephritis with moderate anemia. The marrow showed an increase in the number of staff cells, mitotic normoblasts and reticulocytes.

CASE 11—A woman, aged 34, had marked anemia secondary to chronic glomerular nephritis. Her marrow showed marked increase in the number of normoblasts and reticulocytes without an increase in the number of megaloblasts.

CASE 12—A man, aged 36, with an acute abdominal disturbance caused by chronic lead poisoning, had only moderate anemia, but there were many stippled cells and reticulocytes in the blood. The marrow (fig 2) showed a moderate increase in the number of normoblasts and megaloblasts and large numbers of stippled cells and reticulocytes.

CASE 13—A man, aged 27, had laboratory and clinical findings typical of familial hemolytic icterus, except for the absence of anemia. The marrow showed an increase in the number of normoblasts, megaloblasts and reticulocytes and microcytosis of the mature erythrocytes.

CASE 14—A man, aged 52, had marked splenomegaly and mild anemia. Clinical opinion differed as to whether the diagnosis should be Gaucher's disease or Banti's disease. Absence of Gaucher cells from the marrow favored the diagnosis of Banti's disease, which was confirmed by splenectomy and, later, by necropsy. The marrow showed a marked increase in the number of megaloblasts and a moderate increase in the number of normoblasts, myelocytes and metamyelocytes.

CASES 15, 16, 17 AND 18—Four men, aged 47, 69, 67 and 74, respectively, had pernicious anemia. Before treatment, all had severe anemia with a normal reticulocyte count. The bone marrow, at this time, showed a marked increase in the number of megaloblasts (fig 3), and tended toward a decrease in the number of granulocytes. The marrow of the patient in case 15 showed a moderate increase in the number of normoblasts and reticulocytes. While the patients were under treatment, studies of the marrow were repeated for comparison with the previous findings. The marrow of the patient in case 16, taken at the height of the increase in the number of reticulocytes in the blood, showed a great increase in the number of reticulocytes and normoblasts without much change in the number of megaloblasts.

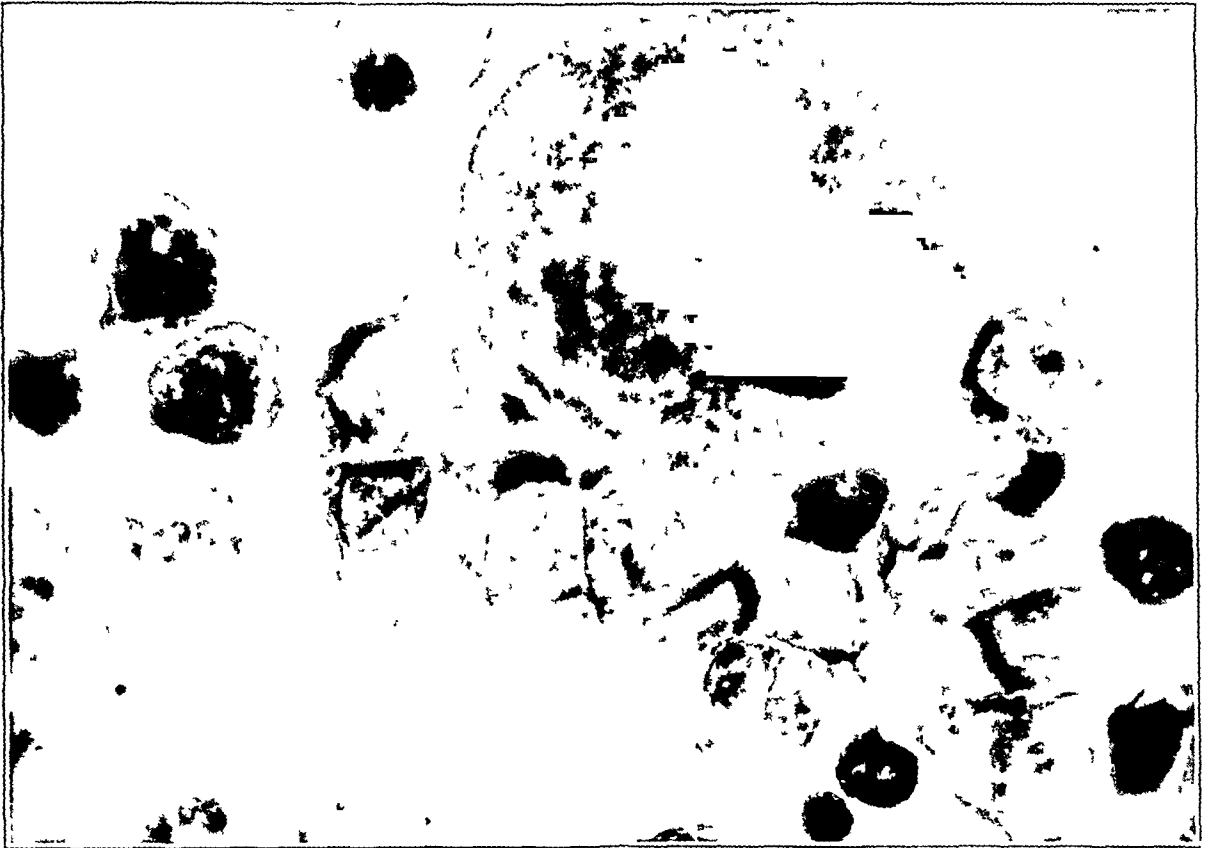


Fig 2 (case 12) —Bone marrow of a patient with lead poisoning, showing a typical megalokaryocyte. Note the megaloblasts.

blasts. The marrow of the patient in case 15, taken ten days after the peak of the increase in the number of reticulocytes, showed a marked decrease in the number of megaloblasts.

CASES 19 and 20—Two men, aged 28 and 17, respectively, had typical Hodgkin's disease. The picture in the marrow was essentially normal.

CASES 21, 22 AND 23—Three women, aged 47, 44 and 49, respectively, had chronic myelogenous leukemia. In all of them, the blood reflected the picture in the bone marrow. The marrow of the patient in case 21 before treatment showed a marked increase in the number of immature granulocytes. Twenty days after 3,216 mg hours of radium was applied over the spleen, the pictures in the blood and marrow were little altered. Studies of the marrow were done in cases 22 and 23 at a time when the blood picture had returned to normal after prolonged

roentgenotherapy. It is interesting to note that the pictures in the marrow were also normal. In case 23, a second study of the marrow was done during a terminal myeloblast crisis. Both the blood and the bone marrow showed a striking increase in the number of myeloblasts.

CASE 24—A girl, aged 7 years, had acute subleukemic monocytic leukemia. The marrow showed a striking picture, with immature cells of the monocytic series replacing the myeloid and erythroid cells.

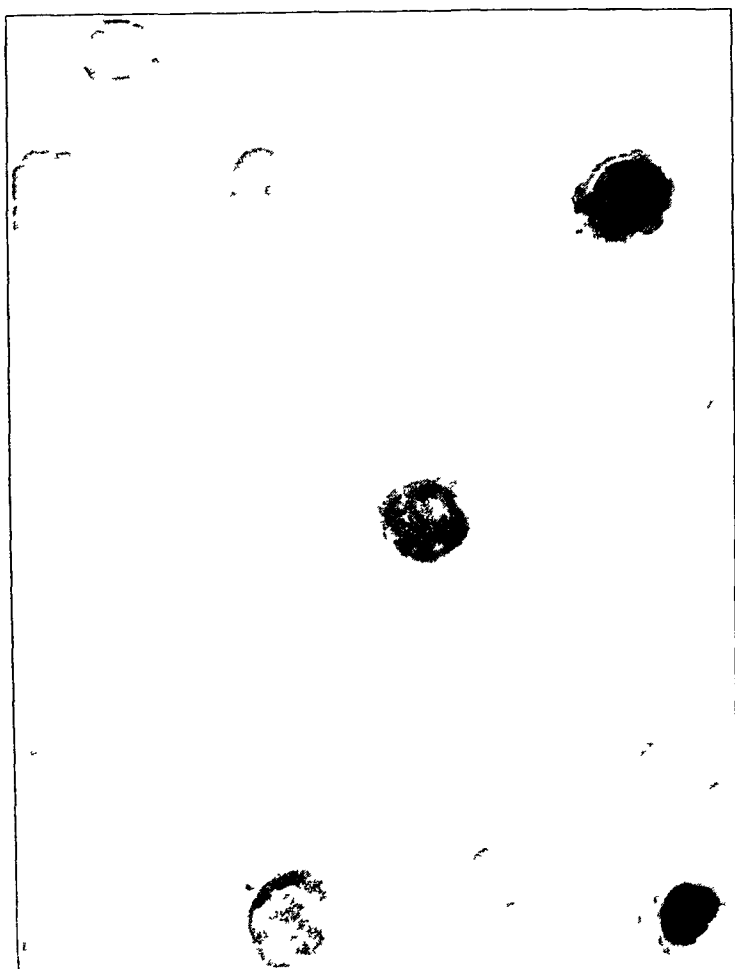


Fig 3 (case 17) —Bone marrow of a patient with pernicious anemia, showing four typical megaloblasts and a multisegmented neutrophil.

CASE 25—A boy, aged 5 years, had xanthomatosis of the Hand-Schüller-Christian type. Sternal puncture was done shortly after death. The marrow showed no typical foam cells. That the sternal marrow was free from xanthomatous infiltration, although it was present in the marrow of other bones and in many other tissues, was shown at necropsy.

CASE 26—A woman, aged 51, had Bence-Jones protein in the urine and multiple defects of the bone. The marrow showed an increase in the number of plasma cells, which favored a diagnosis of multiple myeloma rather than that of a metastatic malignant process.

## COMMENT

Although there are certain limitations to the study of bone marrow obtained by the method of sternal puncture, the method has definite advantages which make it valuable. It aids the experimental hematologist in the study of the origin of blood cells and the physiology of bone marrow and assists the clinician in the solution of some diagnostic problems.

One disadvantage of the method, as pointed out by Peabody<sup>1</sup> and Custer<sup>13a</sup> is that it fails to show the structural relationships which can be seen in fixed sections of the marrow. Another limitation which applies to all methods of obtaining bone marrow for biopsy, is that only a small and not necessarily a representative sample of the entire supply of marrow of the body is obtained. Patchy lesions such as occur in multiple myeloma, Gaucher's disease, Niemann-Pick's disease, xanthomatosis and metastatic malignant processes may be missed, as in our case of xanthomatosis (case 25). However, an increase in the number of plasma cells was found in our case of multiple myeloma (case 26), and Sokolowski<sup>14</sup> found typical cells in a case of Gaucher's disease. Our failure to find Gaucher cells in a case of splenomegaly aided us in making a correct diagnosis of Banti's disease. Therefore, the failure to find typical cells does not necessarily exclude the diagnosis of a patchy lesion, but may be a point against such diagnosis.

The possibility suggests itself that the differential counts on the material aspirated by sternal puncture do not represent the true proportion of the cells in the marrow, either because of dilution with blood or because of a tendency of some cells to be more firmly adherent. From our studies it is evident that error from these sources if it does occur is so slight and relatively constant that it does not detract from the clinical value of the method. If there were much variation in the cellular content of the material obtained, our differential cell counts on marrow from normal subjects would show a greater variation. The myeloid-erythroblast ratio would be high in the marrow of normal subjects if there were much dilution with blood. Our myeloid-erythroblast ratios (3.61:1) fall between those obtained from emulsified, cuffed marrow obtained at necropsy by Schilling<sup>15</sup> (1.21:1) from ten soldiers and by

13a Custer, R. P. Studies on the Structure and Function of Bone Marrow Biopsy, *Am J M Sc* **185** 617 (May) 1933

14 Sokolowski, A. Basophile kugelförmige Gebilde im Milzpunktate im Verlaufe des Morbus Gaucher und die Bedeutung des Sternumpunktates für die Diagnose dieser Erkrankung, *Folia haemat* **46** 281 (Feb.) 1932

15 Schilling, V. Das Knochenmark als Organ. II Die feinere Zytologie des Markparenchyms, *Deutsche med Wchnschr* **51** 344 (Feb. 27) 1925

Doan and Zerfas<sup>16</sup> (9 66 1) from four persons who died as a result of accidents. Because of the presence of blood in the sinuses, all bone marrow obtained for study, including tissue sections, will show some mixture with blood.

The advantages of obtaining biopsy material by sternal puncture are the accurate definition of the morphologic characteristics of the cells and the simplicity of the technic. The clear definition makes it possible to identify each cell accurately, to trace the histogenesis of each cell type and to determine the stage of maturation at which delivery from the bone marrow into the blood occurs. In our material it was possible to trace the development of the erythrocytes and monocytes, as well as that of the granulocytes, from the most mature cell of the series back to a stem cell morphologically similar to the myeloblast. This conflicts with the view expressed by Piney<sup>17</sup> that the megaloblast is not the precursor of the mature erythrocyte, and with some of the many views, summarized by Forkner,<sup>18</sup> concerning the origin of monocytes. The fact that typical megaloblasts were found in almost every specimen of marrow examined also conflicts with Piney's<sup>17</sup> view that the megaloblast is seen only in pernicious anemia. Our observations on mitosis and the delivery of cells agree with those of Sabin<sup>19</sup>. In tracing the maturation of the granulocytes and erythrocytes, mitotic division was observed in cells at least as mature as myelocytes and normoblasts. The absence of metamyelocytes and normoblasts and the presence of staff cells and reticulocytes in the blood and the presence of all these cells in the bone marrow indicate that delivery of the granulocytes and erythrocytes into the blood normally begins at the stage of the staff cell and reticulocyte.

The picture in the marrow enables the clinician to understand more clearly the mechanism of the production of the changes in the blood in disease. In some instances, study of the bone marrow establishes or confirms a diagnosis, and it is often of assistance in planning rational therapy.

In simple leukopenia and in various types of leukocytosis the blood picture accurately reflects the changes in the bone marrow, as illustrated in cases 1, 2 and 3. The picture in the marrow will, however, differ—

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16 Doan, C. A., and Zerfas, L. G. The Rhythmic Range of White Blood Cells in Human, Pathological Leucopenic and Leucocytic States, with Study of Thirty-Two Human Bone Marrows, *J. Exper. Med.* **46** 511 (Sept.) 1927.

17 Piney, A. Nucleated Red Cells Found in Circulation in Pernicious Anemia, *J. Path. & Bact.* **27** 249 (July) 1924.

18 Forkner, C. E. Clinical and Pathologic Differentiation of the Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, *Arch. Int. Med.* **53** 1 (Jan.) 1934.

19 Sabin, Florence R. The Bone Marrow, *Physiol. Rev.* **8** 191 (April) 1928.

entiate simple leukopenia from aplastic anemia and aleukemic leukemia and probably from essential granulopenia (agranulocytic angina). It should aid in distinguishing leukocytosis of a leukemoid type from true leukemia.

In cases of anemia, sternal puncture gives much valuable information. In aplastic anemia the diagnosis can be definitely established (case 4), and the first evidence of retuning function of the marrow should be readily detectable. An increase in the number of normoblasts is the most characteristic feature of the marrow in anemia due to chronic hemorrhage (cases 5 and 6), infections (cases 7, 8, 9, 10 and 11), toxins (case 12) or hemolytic icterus (case 13). This hyperplasia of the marrow is reflected by evidence of rapid regeneration of the red cells in the blood in lead poisoning (case 12) and in hemolytic icterus (case 13) but such evidence of regeneration is slight or absent in chronic hemorrhage and in infection. In the case of congenital syphilis (case 7) the blood picture suggested aplastic anemia. Brown and Roth<sup>20</sup> and Osgood and Haskins<sup>21</sup> pointed out that the blood picture in anemia of nephritis suggests decreased activity of the bone marrow. This apparent discrepancy between the findings in the blood and those in the marrow supports Witts'<sup>22</sup> statement that "hyperplasia of the marrow is by no means synonymous with increased blood formation, the reaction is often abortive and the cells fail to mature." The finding of numerous stippled erythrocytes in the marrow in lead poisoning (case 12) does not agree with the opinion of Aub and his associates<sup>23</sup> that basophilic stippling does not occur in the marrow. The finding of basophilic stippling in most specimens of bone marrow studied suggests that this is a sign of immaturity, not of degeneration, and can be used, as are polychromatophilia and reticulocytosis, to indicate an increased rate of regeneration of red cells.

In untreated pernicious anemia (cases 15, 16, 17 and 18) the most characteristic change in the marrow is an increase in the number of megaloblasts. This observation agrees with the findings of Peabody<sup>3</sup> in seven cases of Arinkin<sup>7a</sup> in ten cases, of Barta<sup>6c</sup> in twenty-two cases, of Tempka and Braun<sup>6e</sup> in thirty cases and of Holmes and Brown.<sup>7</sup> As reported by Tempka and Braun, a few multilobulated

20 Brown, G. E., and Roth, G. M. The Anemia of Chronic Nephritis, *Arch Int Med* **30** 817 (Dec.) 1922.

21 Osgood, E. E., and Haskins, H. D. Causes, Classification, and Differential Diagnosis of Anemias, *Ann Int Med* **5** 1367 (May) 1932.

22 Witts, L. J. Pathology and Treatment of Anemia (Goulstonian Lectures), *Lancet* **1** 495 (March 5), 549 (March 12), 601 (March 19) and 653 (March 26) 1932.

23 Aub, J. C., Fairhall, L. T., Minot, A. S., and Resnikoff, P. Lead Poisoning, *Medicine* **4** 1 (Feb-May) 1925.

neutrophils and giant staff cells are present. No cell type is specific for pernicious anemia, although as a whole the picture in the marrow has diagnostic value. With treatment, the picture reverts to normal and studies of the marrow add little to the information obtainable from studies of the blood.

Studies of the marrow in Hodgkin's disease (cases 19 and 20) are of no diagnostic value. No support was found for Medlar's<sup>24</sup> view that there is a proliferation of the megalokaryocytes in Hodgkin's disease.

In leukemia, the picture in the marrow is very interesting. In typical cases (cases 21, 22 and 23), in treated or untreated patients the pictures in the marrow and in the blood are similar. In aleukemic and sub-leukemic cases, study of the marrow should be of great diagnostic value (case 24).

Many problems for investigation are suggested by this study. A larger series of normal subjects and a greater number of patients with each pathologic condition should be studied. Infectious mononucleosis, essential granulopenia, malaria and other conditions remain to be investigated. Red cell counts, white cell counts and estimations of the hemoglobin content should be done on the oxalated marrow. The action on the marrow of various agents, such as nucleotides, adenine sulphate, roentgen rays, amidopyrine and benzene, may be studied. The material obtained by sternal puncture should be suitable for tissue culture.

#### CONCLUSIONS AND SUMMARY

1. A clinically practical method, modified from Atkinson, of obtaining bone marrow for biopsy by sternal puncture is described.

2. The simplicity of the technic and the accurate definition of cell morphology possible in the tissue so removed make this a valuable method for the study of the histogenesis of the blood cells and of the physiology of the bone marrow and for diagnosis.

3. The loss of structural relationships in marrow so removed is the only limitation of the method that does not apply to other methods of obtaining marrow from biopsy.

4. Differential, peroxidase and reticulocyte counts on the sternal marrow of twenty-eight healthy men and twenty-six patients with fifteen disorders of the hematopoietic system are reported and discussed.

5. Evidence was found that monocytes are derived from a stem cell (monoblast) similar in morphology to the myeloblast, that megal-

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<sup>24</sup> Medlar, E. M. An Interpretation of the Nature of Hodgkin's Disease, *Am J Path* 8:499 (Sept.) 1931.

blasts are precursors of normoblasts and are not the specific cell of pernicious anemia and that basophilic stippling occurs in the marrow

6 Study of the sternal marrow established the diagnosis of aplastic anemia and subleukemic monocytic leukemia, and it aided in the differential diagnosis of Banti's disease from Gaucher's disease, of anemia of congenital syphilis from aplastic anemia and aleukemic leukemia and of multiple myeloma from a metastatic malignant process

7 Other problems which may be solved by this method are suggested

NOTE—Since this article was written and the method was demonstrated at the Scientific Exhibit of the Eighty-fifth Annual Meeting of the American Medical Association in Cleveland, the method has been in regular use in a number of clinics, where its clinical practicability and diagnostic value have been demonstrated. We have studied the sternal marrow from over twenty-five additional patients. The method has proved especially valuable in the diagnosis of aleukemic myelosis and lymphadenosis. In malaria all stages of phagocytic digestion were observed in the bone marrow, a process which has not been observed to occur in the blood. A larger percentage of the erythrocytes in the marrow contained malaria parasites than of the erythrocytes in the blood, which was drawn at the same time. In infectious mononucleosis the typical large lymphocytes were demonstrated to be present in the marrow as well as in the blood.



# EFFECT OF LIGHT MUSCULAR TRAINING ON PATIENTS WITH HEART DISEASE

RHEUMATIC HEART DISEASE, CHANGES AT REST AND DURING  
EXERCISE

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AND

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In recent years there have been numerous studies dealing with the effect of exercise on patients with heart disease. These studies have dealt almost exclusively with single acute experiments. While it is generally assumed that training increases one's capacity for work through the development of skeletal muscles, heart and lungs and better coordination of movements, so little is known about the effect of repeated exercises on patients with heart disease that there is a pronounced difference of opinion among cardiologists as to how harmful or beneficial such exercises are. The facts are few. The results of experiments with single exercises are not applicable. It was thought that by repeating a certain form of exercise over a period of several weeks, differences between people with normal hearts and those with diseased hearts, which were obscured in single exercises, might make themselves manifest. This refers only to patients with no evidence of failure of the right or left side of the heart and eliminates from consideration patients who are convalescing from heart failure.

The work of Oertel<sup>1</sup> and Schott,<sup>2</sup> which purports to demonstrate marked benefits from planned exercises, does not stand critical analysis. They judged improvement chiefly by subjective response on the part of the patient. Patients reported that they felt better, and they seemed to perform the more or less simple exercises with greater ease. Such evidence, while suggestive, is not conclusive. Among clinicians in general there are chiefly impressions, and these vary greatly, as to the rôle which exercise plays in patients with heart disease whose hearts are said to be "well compensated."

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1 Oertel, M J Die diätetisch-mechanische Behandlung der chronischen Herzmuskelerkrankungen, Vienna, Zeit- u Streitfragen, 1889

2 Schott, T Physikalische Behandlung der chronischen Herzkrankheiten, Berlin, Julius Springer, 1916

For this study six patients with rheumatic heart disease were selected. They were between 18 and 22 years of age. Three of them had mitral stenosis and regurgitation with aortic insufficiency. The other three had only mitral stenosis and insufficiency. In one of the latter there was auricular fibrillation. The other five patients had normal rhythm. In one patient, a teleoroentgenogram showed only a bulge in the region of the left auricle. In the other patients, there was definite moderate enlargement of the heart both to the right and to the left. None of the patients showed evidence of failure of the right or left side of the heart. There was no sign of active infection. As controls, two people, aged 22 and 24, respectively, who had no evidence of heart disease and who were otherwise considered normal were studied.

Before and during the training period, usually from five to six weeks, frequent observations were made during rest under basal conditions on the following: pulse rate, respiratory rate, oxygen consumption, respiratory minute volume, cardiac output, velocity of blood flow, vital capacity, breath-holding ability, electrocardiograms and teleoroentgenograms. During exercise, changes were observed in pulse rate, respiratory rate, respiratory minute volume, blood pressure, oxygen consumption, velocity of blood flow, mechanical efficiency and lactic acid in the venous blood.

#### METHOD

The exercise was performed on a stationary bicycle designed by D. B. Dill of the department of biochemistry, Harvard University. It was of the Prony-brake type, with an automobile brake band and a cast-iron flywheel. The tension of the band on the drum was controlled by a screw adjustment which made it possible to keep the load constant in spite of changes due to the variations in friction. Such variations occurred especially at the beginning of exercise. The bicycle had a gear ratio of 1:2.2. A speedometer was attached to measure distance. During the first three days, before any exercise was begun, basal values were obtained. During the next three days, the patients pedaled on the bicycle for only ten minutes each day. Thereafter, all except the first two patients pedaled each day for one hour in the morning and one hour in the afternoon. The first two patients pedaled for six weeks, only one hour each day. Four of the patients continued the exercise for from four to six weeks, one for two weeks, another for fifteen weeks. Occasional short walks were also taken. The two patients who pedaled only one hour daily began their exercise by pedaling with each foot thirty times a minute (66 revolutions of the flywheel) against a pull of  $2\frac{1}{2}$  pounds (1,133.97 Gm). This corresponded to 82.2 Kg meters work per minute. The rate of pedaling was timed by a metronome. At the end of the first week of training the load was increased to 4 pounds (1,814.37 Gm) at 66 revolutions per minute, the third week, 4 pounds (1,814.37 Gm) at 88 revolutions and thereafter, 5 pounds (2,267.96 Gm) at 115 revolutions per minute. The procedure was much the same for the other patients except that the pedaling was done for two hours daily, one hour in the forenoon and one hour in the afternoon, in the first two weeks with a pull of 4 pounds at 88 revolutions per minute, the third week, 5 pounds at 88 revolutions, the fourth week, 5 pounds at 95 revolutions, and the fifth week, 6 pounds (2,721.55 Gm) at

115 revolutions, for two hours, and 6 pounds at 154 revolutions for ten minutes. The patient who trained for fifteen weeks pedaled, after the fifth week, for two hours daily against a pull of 6 pounds at 154 revolutions per minute.

Oxygen consumption was measured, using a 125 liter Tissot spirometer. Cardiac output was determined by means of the acetylene method of Grollman.<sup>3</sup> Sodium dehydrocholate (10 cc ampules) was used as a means of measuring the circulation time from the cubital vein to the tongue.<sup>4</sup> Three injections of from 3 to 4 cc each were given within three minutes. The measurements of the velocity of blood flow during exercise were made between the eighteenth and the twenty-first minute of exercise. The duration of the injection was between two and one-half and three seconds. The readings recorded are from the end of the injection. Subjective disturbances mentioned by Winkler<sup>5</sup> as likely to occur were not observed. Respiratory and pulse rates were obtained while the patients were breathing into the spirometer. The samples which were collected for gas analysis and estimation of oxygen consumption during exercise were always of the expired air for the three minutes between the seventh and tenth minutes of exercise. It was found, by measuring the oxygen consumption at various times during the hour of exercise, that in this period between the seventh and tenth minutes oxygen consumption had reached a steady state. During the heavier work, oxygen consumption was measured for only two minutes between the seventh and ninth minutes.

For studies of mechanical efficiency, oxygen consumption was measured between the twenty-seventh and thirtieth minutes, and the work was then increased by  $1\frac{1}{2}$  pounds (680.38 Gm) while the subject was pedaling, everything else remaining unchanged. With the original work as the base line, the net efficiency was calculated from the excess oxygen required to pull the added  $1\frac{1}{2}$  pounds a measured distance. The heart rate was measured by counting for a full minute, the cardiac impulse, by palpation.

During the faster pedaling with greater work (a pull of 6 pounds at 152 revolutions per minute, 455 Kg meters per minute), venous blood was taken between the ninth and tenth minutes during exercise for estimation of lactic acid. The method used for measuring the lactic acid was that of Friedemann, Cotonio and Shaffer.<sup>6</sup> The room temperature during the experimental procedure varied no more than 3 C from day to day.

## RESULTS

*Changes at Rest Pulse Rate, Respiratory Rate and Pulmonary Ventilation*—The pulse rate during rest under basal conditions on three successive days before training was between 55 and 60 per minute in the two normal persons. In the patients with heart disease the rate varied from 58 to 82, although in each patient it was practically the same on the three successive days. In all the patients the pulse rate

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3 Grollman, A. Determination of the Cardiac Output of Man by the Use of Acetylene, *Am J Physiol* **88** 432, 1929.

4 Winternitz, M., Deutsch, J., and Brull, Z. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, *Med Klin* **27**:986, 1931.

5 Winkler, L. Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, *Med Klin* **28** 83, 1932.

6 Friedmann, T. E., Cotonio, M., and Shaffer, P. A. Determination of Lactic Acid *J Biol Chem* **73** 335, 1927.

during rest, taken twice weekly, remained unchanged throughout the period of training

In only one of the patients was the respiratory rate definitely changed. This was the patient (C P) in whom the most marked training effect<sup>7</sup> was observed. In this patient, the respiratory rate gradually decreased during the first month of training from 15 to 10 per minute. As in the other patients, there was no significant change in pulmonary ventilation.

*Oxygen Consumption, Arteriovenous Oxygen Difference and Cardiac Output*—The oxygen consumption under basal conditions showed no essential change in any of the patients. Such results would be explained by Schneider and Foster<sup>8</sup> as due to a counterbalance between the new production of protoplasm and an increase in cellular efficiency, one tending to lower, the other to raise, the basal metabolic rate. The exer-

TABLE 1—*Changes in Cardiac Output During Training in a Patient with Rheumatic Mitral Stenosis and Insufficiency*<sup>a</sup>

Duration of Training	Oxygen Consumption, Cc per Minute	Arteriovenous Oxygen Difference, Cc per Liter	Cardiac Output, Liters per Minute
1 week	212	73.9	3.5
2 weeks	221	75.8	3.4
4 weeks (day before hemoptysis)	217	89.8	2.6
Following day (exercise stopped)	226	105.8	2.1
4 days later	212	67.2	3.1

<sup>a</sup> The exercise had to be discontinued because of the development of hemoptysis.

cise, however, was hardly severe enough to make these factors of real significance.

In one patient (T McK), the cardiac output showed an interesting change. After exhibiting practically no training effect, this patient began in the fourth week of training to experience discomfort while pedaling. Observations made during exercise showed a poor response to the work. The training was discontinued when he experienced a tightness across the chest and a cough with a slight hemoptysis while pedaling. In this case, the cardiac output per minute before training was 3.2 liters, after one week it was 3.5 liters, and after three weeks it was 3.4 liters. The day before the hemoptysis it was 2.5 liters, the day after, 2.1 liters. After four days, during which time the patient did not exercise, the cardiac output was 3.2 liters. The diminution in the cardiac output of this patient was associated with an increase in arteriovenous oxygen difference, as can be seen in table 1.

7 Here, as elsewhere, "training effect" is meant to indicate an improvement in response to exercise.

8 Schneider, E. C., and Foster, A. O. Influence of Physical Training on the Basal Metabolism Rate of Man, *Am J Physiol* 98:595, 1931.

The cardiac output in the normal subjects, as well as in the patients with heart disease, was strikingly constant. In one of the normal persons, for example, the cardiac output per minute at rest and before training was 3.7 liters, with the arteriovenous oxygen difference, 57.4 cc per liter and the oxygen consumption, 210 cc per minute. At the end of training the cardiac output was 3.5 liters, with the arteriovenous oxygen difference, 57.5 cc per liter and the oxygen consumption, 204 cc per minute. In one of the patients with mitral stenosis the cardiac

TABLE 2—*Velocity of Blood Flow at Rest (from Cubital Vein to Taste Buds of Tongue)*

Name	Diagnosis	Before Training, Seconds			During Training, Seconds					
					1st Week	2d Week	3d Week	4th Week	5th Week	6th Week
C P	Mitral stenosis, aortic insufficiency, normal rhythm	16	14	15½	15	16	17	17		18½
			14		17	16	19	18	16½	
			13		16	18	17	17	19½	17½
		Average	16	14	15½	16	17	18	17	18
P B	Mitral stenosis, aortic insufficiency, normal rhythm	13	12	13	15	19	19	22	20	
		15	13	15	16	20	21	20	22	
		14	12	14	18	21	20		22	
		Average	14	12	14	16	20	20	21	22
J L	Mitral stenosis, aortic insufficiency, normal rhythm	14	17	15	17	17	17	17	19	22
				17	18				22½	24
		17		17	18½					
		Average	16	17	17	18	17	17	21	23
B B	Mitral stenosis, auricular fibrillation			24½	25½	24				
					29	27				
				28½	27½					
		Average		27	27	26				
R V	Normal	17		16	16	18	11½	13½	16	
		13½		15	16	15	15½	16		
				17	17	16	15			
		Average	15	16	16	16	14	15	16	

output, taken repeatedly before and during the five weeks of training, varied only from 3.5 to 3.7 liters. The variations in the cardiac output in the other patients were only slightly greater and showed no definite rise or fall during the period of training.

*Velocity of Blood Flow*—The speed of circulation, as measured by the sodium dehydrocholate method during rest, was within normal limits in all the patients except the one with auricular fibrillation. In this case, contrary to what was reported by Winternitz, Deutsch and Brull,<sup>4</sup> the time of circulation was definitely prolonged (table 2).

The sodium dehydrocholate method for the measurement of the velocity of blood flow was generally satisfactory. However, the measure-

ments taken at rest were definitely less reliable than those taken during work. There was a sharper and more distinct taste during exercise than at rest, and the three measurements taken with each ampule of the sodium dehydrocholate checked more closely in exercise. Perhaps this is to be accounted for on the basis of a more rapid flow during exercise. However, in four of the patients and one of the normal subjects satisfactory results were obtained. The results in these cases are presented in table 2. A definite general training effect during exercise was observed in the three patients with regular rhythm. In these patients there was a slowing of the velocity of blood flow at rest. In the normal subject and in the patient with auricular fibrillation the general improvement during exercise was only slight. In these two subjects, no definite change in the velocity of blood flow at rest was observed. In the patient with auricular fibrillation, the exercise was continued for only two weeks.

*Vital Capacity and Breath Holding*—Vital capacity and breath holding are considered together, although they are not necessarily tests of the same significance. It is our impression that measurement of the vital capacity is a greater aid in the study of cardiac function than is the estimation of the length of time the breath can be held. Breath-holding ability has certain variables which are not always easily controlled.<sup>9</sup> The subjective response to the stimulus for breathing may conceivably vary with practice. Also to be considered is the fact that many patients learn more or less subconsciously to breathe deeply a few times before they hold their breath. In this way the initial alveolar carbon dioxide content is lowered, and the patient is enabled to hold his breath longer. However, if satisfactory precautions are taken, breath holding may be of some value as an index of cardiac function, probably chiefly because of its relationship to the vital capacity of the lungs.

In the two normal subjects, the vital capacity remained unchanged during the period of training. The results in one of these are presented in figure 1. In two of the patients, however, slight but definite increase in the vital capacity was observed during the training period. In these two patients, a definite improvement in response to exercise was observed during the period of training. The single readings for vital capacity represent in each instance the maximum of three readings. The breath holding in these fairly well controlled cases was observed generally to parallel the vital capacity.

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9 Palcso, B. Der Wert der Zeitdauer des Atemhaltenkönnens in der funktionellen Herzdiagnostik, *Ztschr f Kreislaufforsch* **20** 457, 1928. Katz, L. N., Hamburger, W. W., and Rubinfeld, S. H. Observations on the Effect of Oxygen Therapy. Changes in the Circulation and Respiration, *Am J M Sc* **184** 810, 1932.

*Electrocardiograms*—In one of the patients, no change was observed in the electrocardiogram. This was one of the two patients with involvement of only the mitral valve who showed no training effect during exercise. In the three patients who showed a definite effect, the following changes were noted: in one, a slight increase in the height of the P wave in lead II, and in the others (J L and C P) an increase in the height of the T waves, as shown in the electrocardiogram. In the patient who had a slight hemoptysis there was, following the hemoptysis, an increase in the P R interval from 0.16 to 0.18 second, and although the axis of the QRS wave remained unchanged, the P waves changed,  $P_2$  becoming less prominent and  $P_3$  wholly inverted,

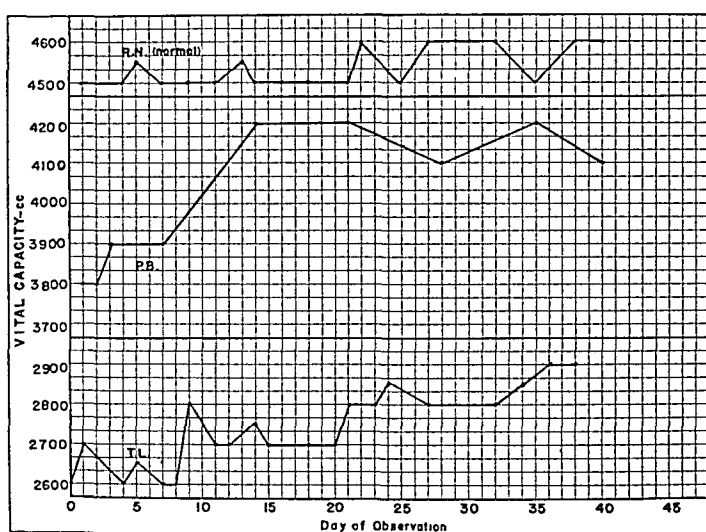


Fig 1—Changes in vital capacity occurring in one normal subject and in two patients with mitral and aortic valvular disease. The days indicate the period of training.

as shown in the electrocardiogram. We are unable to explain the significance of this change.

*Teleoroentgenograms*—Teleoroentgenograms were taken on three successive days before exercise was begun, one was taken weekly throughout the period of training, and three were again made at the end of training. Small variations in cardiac measurements were seen in the three teleoroentgenograms before exercise was begun, probably owing to slight changes in position, the period of respiration, etc. Changes greater than what might be considered normal variations did not occur during the period of training. While the exercise was perhaps not severe enough or of sufficient duration to cause changes in the size of the heart, it seemed to us that slight changes might occur, especially in the size of the left auricle in the case of mitral stenosis. Careful measurements, however, failed to reveal such changes.

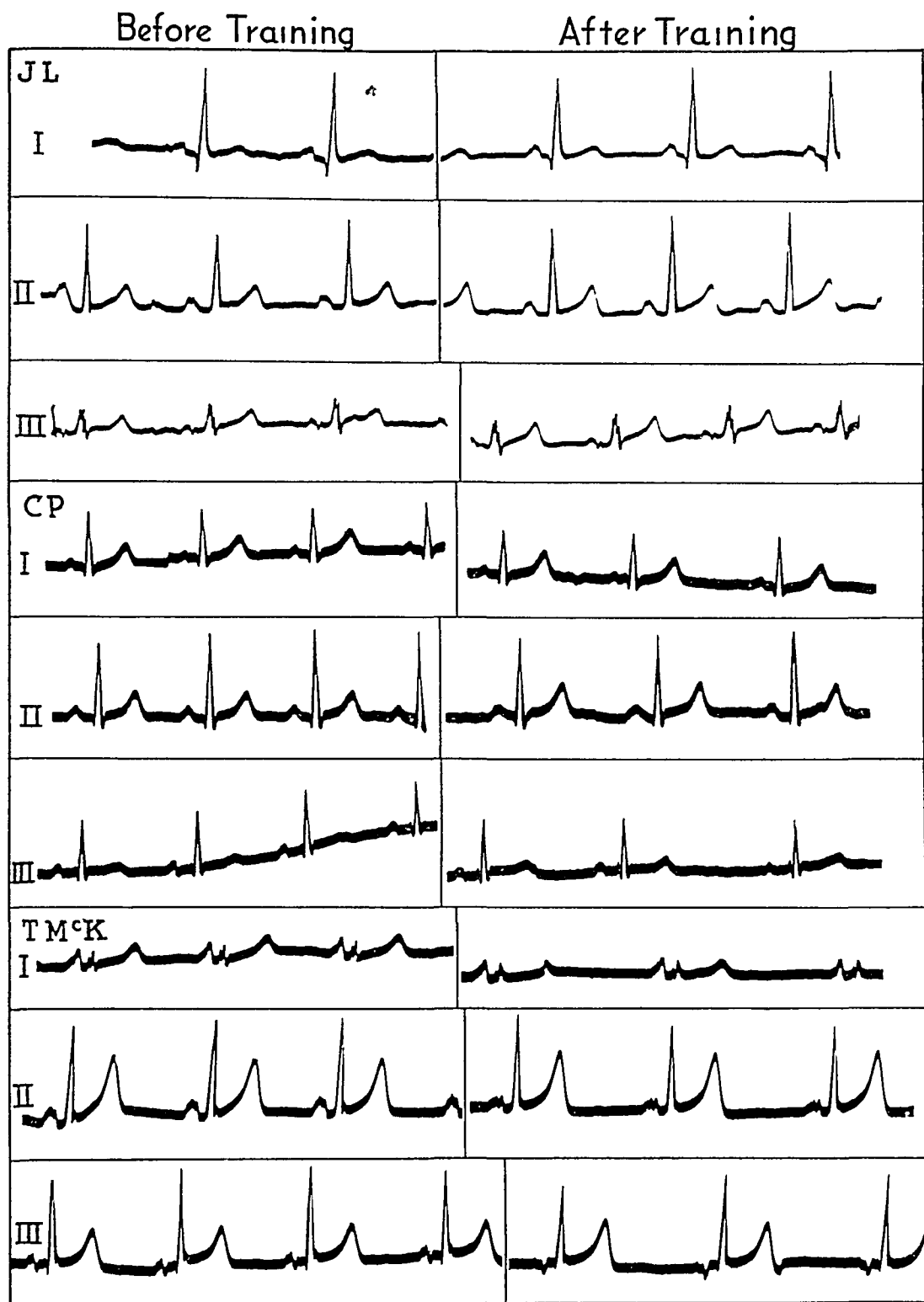


Fig 2—Electrocardiograms taken before and after training, showing, in the cases of J L and C P, an increase in the height of the T waves and in the case of T McK a slight increase in the P R interval, lowering of  $P_2$  and inversion of  $P_3$ .



## CHANGES DURING EXERCISE

In general, it may be said that in the two normal people there was a slight training effect, in the three patients with disease of both aortic and mitral valves, a definite and rather marked training effect, in the two patients with only mitral disease and with regular rhythm, no training effect, and in the one patient with mitral stenosis and auricular fibrillation, a slight effect. In one of the two patients with mitral stenosis and regular rhythm, the training had to be discontinued during the fourth week because of the development of a feeling of tightness across the chest and a slight hemoptysis. The various types of response are recorded in the charts.

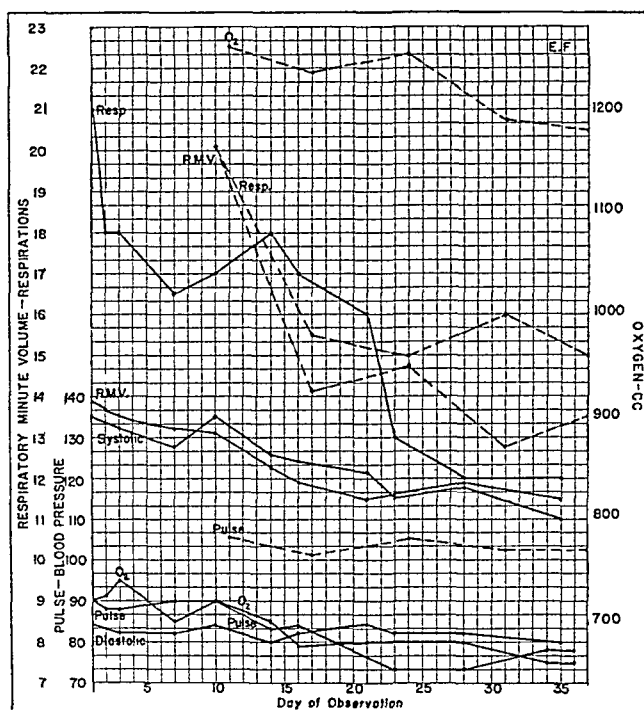


Fig 3—Changes occurring during exercise in a normal subject. In the first three days the exercise consisted of pedaling on a stationary bicycle for ten minutes daily, thereafter for one hour twice daily. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

Figure 3 represents the changes which occurred in one of the normal persons. The other normal person did not differ essentially in his response. There was a slight training effect, an effect of about the magnitude which might be expected in a normal person with the exercise which we studied. Within the first three weeks, the oxygen consumption for the lighter work dropped from 720 to 680 cc per minute, the respiratory minute volume, from 13.85 to 11.5 liters, the blood pressure, from 136 systolic and 84 diastolic to 110 systolic and 80 diastolic, the pulse rate, from 90 to 74 per minute and the respiratory rate, from 21 to 13 per

minute There were corresponding changes during the heavier work These results in a normal person correspond to those reported by Gemmill, Booth and Pocock<sup>10</sup>

Figure 4 represents the most striking training effect which we observed The patient had mitral stenosis and insufficiency and aortic

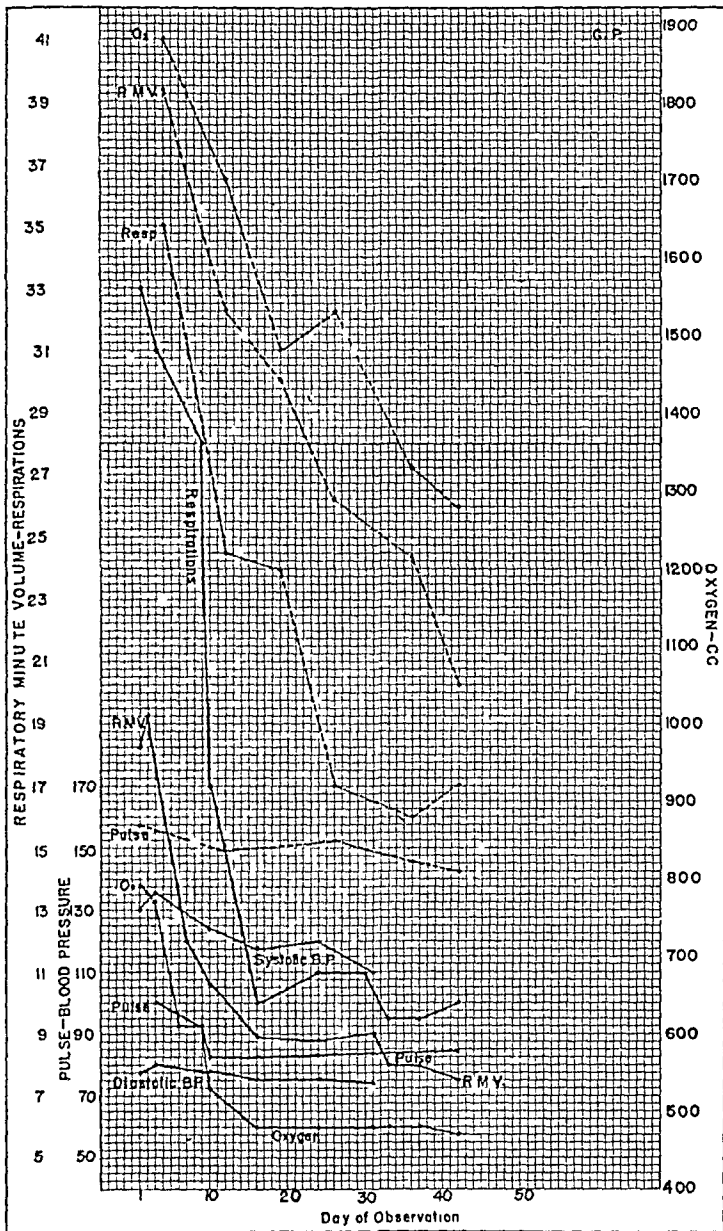


Fig 4—Changes occurring during exercise in a patient with rheumatic mitral and aortic valvular disease During the first three days of observation pedaling on a stationary bicycle was carried out for ten minutes daily, and thereafter for one hour daily The dotted lines represent changes during heavier work and the solid lines, changes during moderate work

10 Gemmill, C , Booth, W, and Pocock, B Muscular Training Physiologic Effect of Daily Repetition of Same Amount of Light Muscular Work, Am J Physiol 92 253, 1930

insufficiency, moderate cardiac enlargement to both the right and the left and definite enlargement of the left auricle. It is noted that there was a marked change in the cardiovascular response to the same exercise as the training was continued to the forty-second day. The changes during the first three days must be taken to be due chiefly to overcoming excitement and awkwardness, inevitably associated with the exercises at the beginning. (On these days the patients rode for only ten minutes.) Beyond these first few days, however, the changes must be due to adjustments in the cardiovascular apparatus and lungs. It might be noted here that this patient was a very calm, husky, athletic youth who had been living a fairly active life (swimming, playing handball and hiking) just before our studies were begun. Most of the improvement in performing the light work had taken place at the end of sixteen days. Thereafter, the changes were only slight. In these sixteen days, the oxygen consumption per minute during exercise dropped from 790 to 480 cc, the respiratory rate from 33 to 10 per minute, the pulse rate from 100 to 82 per minute, the blood pressure from 130 systolic and 78 diastolic to 110 systolic and 74 diastolic and the respiratory minute volume from 18.25 to 8.9 liters. In the heavier exercise (represented by the dotted lines) the changes were of similar magnitude, only the pulse rate changed relatively less, from 158 to 142 per minute. However, since 158 approaches the maximum pulse rate obtainable during exercise, it is likely that this initial rapid pulse rate represents a restricted level, owing to the factors which limit increasing pulse rate beyond a certain level, whereas the final rate of 142 represents a straight rise to that figure. Thus, real differences in the response of the pulse rate may be obscured at such levels.

Figure 5 shows the changes which occurred in the patient with mitral stenosis and insufficiency in whom the exercise had to be discontinued because of the development of hemoptysis. There was relatively little change during the early stage of training. After the fourth day, which in this instance corresponded to the day when training was begun, to the twenty-seventh day, the pulse rate, systolic and diastolic blood pressures and oxygen consumption remained practically constant. After the twenty-seventh day they rose gradually, indicating a less efficient response to the exercise, until the training was discontinued on the thirty-second day because of hemoptysis. The failure of this patient to improve with exercise is as definite as the marked improvement in the previous patient presented. Another patient with only mitral disease also showed no improvement with exercise, although he did not give evidence of being any the worse for the exercise.

Figure 6 shows the changes which took place over a period of fifteen weeks in a patient with aortic and mitral valvular disease. For the

first twenty-two days there was a distinct improvement in the circulatory and respiratory response to exercise. Then for a few days the reverse effect took place, the pulse rate, oxygen consumption, respiratory rate, etc., increasing, although the work remained the same. After a few days this paradoxical change disappeared, and the previous level of

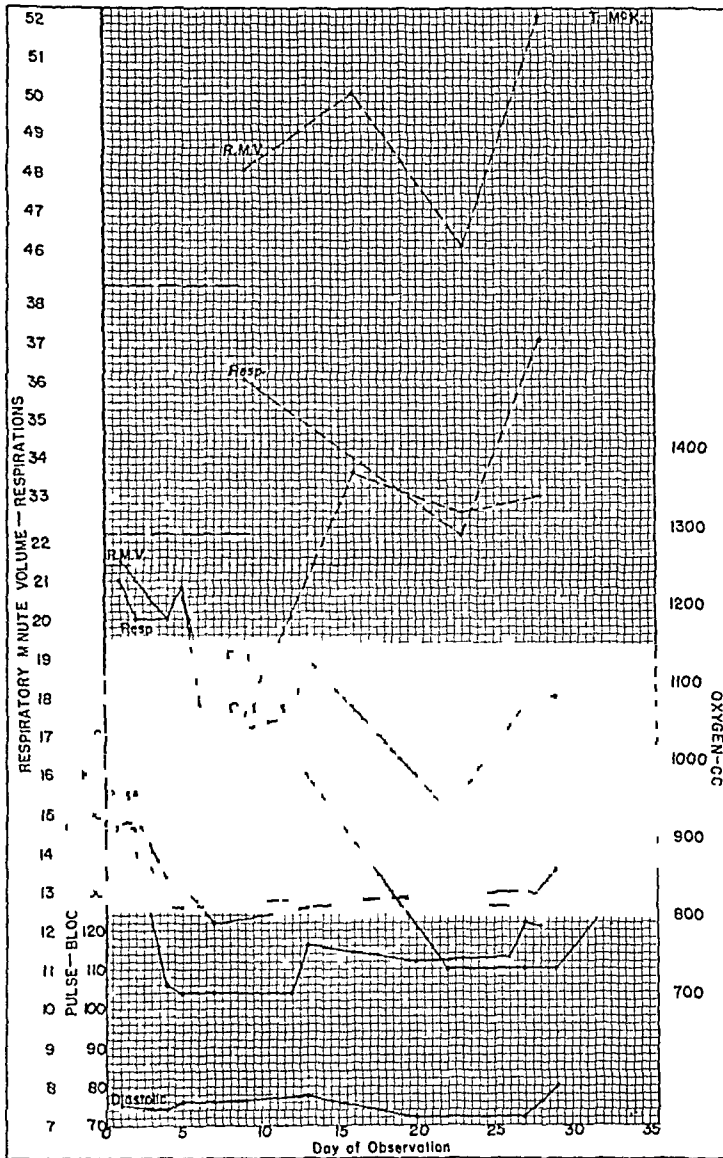


Fig 5—Changes occurring during exercise in a patient with rheumatic mitral disease. In the first four days the exercise was for ten minutes daily, and thereafter for one hour twice daily. On the thirty-second day exercise was discontinued because of the development of hemoptysis. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

response was reached and maintained thereafter. This loss, as it were, of training effect for several days was demonstrated by the results of several experimental periods, so that the change cannot be attributed to an experimental error. During this period there was no evidence of

undue excitement or tension on the part of the patient. In the evening of the eighty-sixth day of exercise, this patient showed a moderately severe pharyngitis with a temperature of 101 F. He remained in bed for two and one-half days, during which time the exercise was discontinued. When exercise was resumed on the ninetieth day, there was no indication that the infection had impaired his response to exercise.

*Velocity of Blood Flow*—In figure 7 are shown the changes in the velocity of blood flow during exercise in the course of training in the three patients who had a distinct training effect and in one normal subject. In the normal subject, the velocity was slowed from ten and a

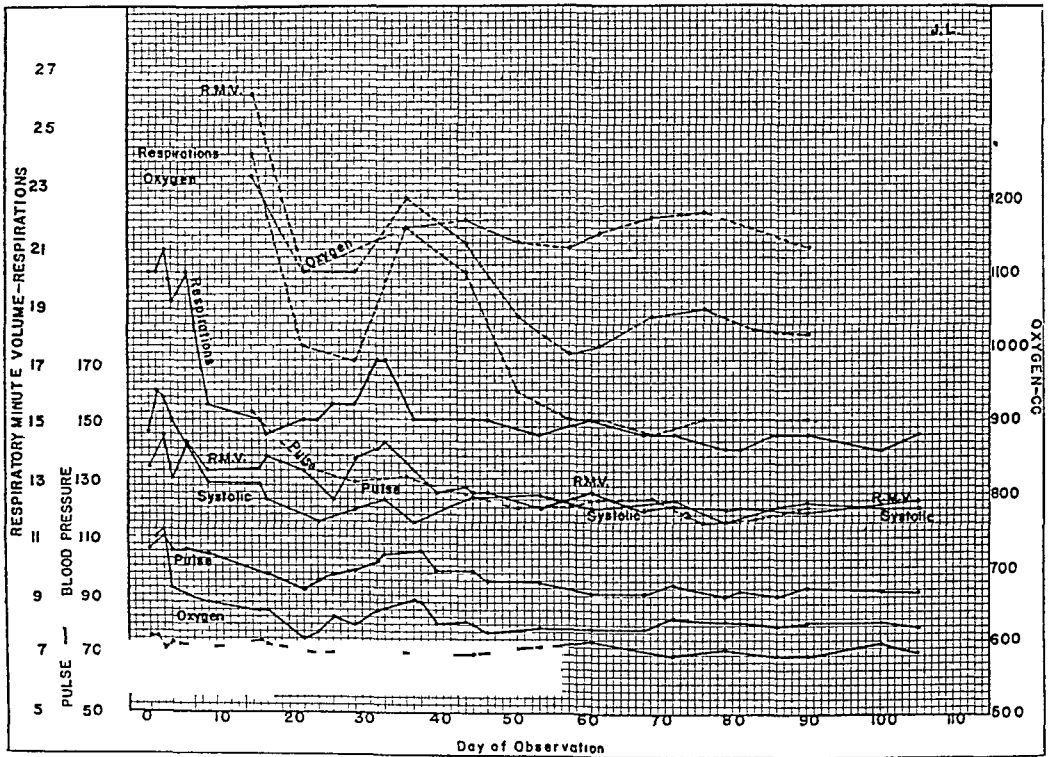


Fig 6—Changes occurring during exercise in a patient with rheumatic and aortic mitral disease. In the first three days the exercise was for ten minutes daily, and thereafter for one hour twice daily. The dotted lines represent changes during heavier work and the solid lines, changes during moderate work.

half to sixteen and a half seconds. In the patients there was also a distinct slowing of from three to four seconds over a period of from four to five weeks. As noted previously, the sodium dehydrocholate method proved especially satisfactory during exercise, the results of three successive injections within a few minutes rarely varying more than one second. For example, in the case of P. B. the following results were obtained on the six occasions when the velocity of blood flow was measured during exercise: (1) ten seconds, (2) ten, nine and one-half and ten seconds, (3) ten and one-half, eleven and eleven seconds, (4)

eleven and one-half, eleven and one-half and eleven and one-half seconds, (5) twelve, thirteen and thirteen seconds and (6) thirteen and one-half, fourteen and thirteen and one-half seconds. In the patient with auricular fibrillation, the velocity of blood flow during exercise and at rest was unusually slow. During the three weeks in which this

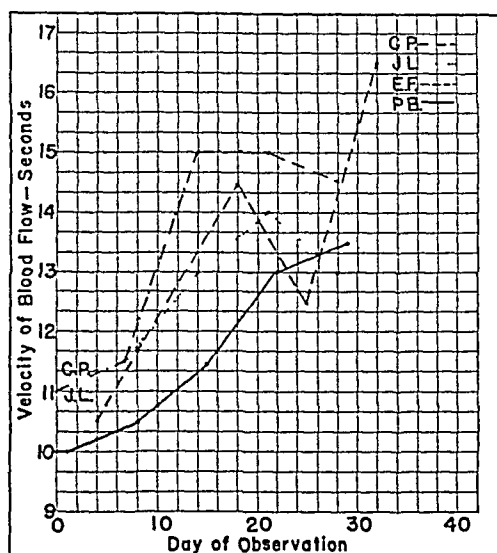


Fig 7—Velocity of blood flow in exercise

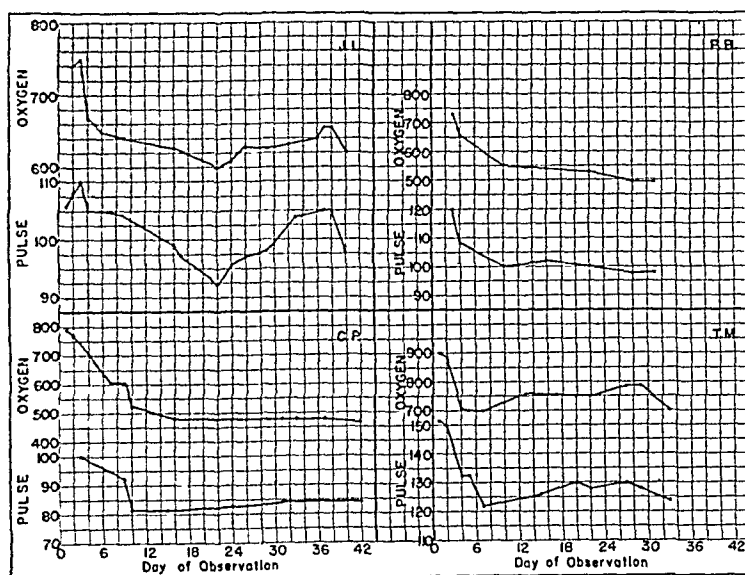


Fig 8—Changes in the pulse rate and consumption of oxygen during exercise in four patients. Note the striking parallelism.

patient trained, the time of circulation from the cubital vein to the taste buds of the tongue remained between twenty-one and twenty-three seconds. During this time only a slight general improvement in cardio-respiratory response was noted, as measured by the other tests of this study. In the two patients who showed no improvement in exercise,

the velocity of blood flow during exercise remained unchanged throughout the period of training, the difference in one patient being one second, and in the other patient two seconds, between the first and last estimations

*Pulse Rate*—An interesting observation is recorded in figure 8. It may be noted that there was a striking parallelism between the pulse rate and the oxygen consumption during exercise throughout the period of training. As the pulse rate became slower during the same exercise, the oxygen consumption dropped. Usually we were able to predict, from a change in pulse rate, a change in oxygen consumption. The pulse rate was found not to be as effective an index of mechanical efficiency when it was measured simply in the resting state, or even when the length of time required for it to return to a resting state after exercise was measured. These two measurements were found to be distinctly more variable than the measurement of the pulse rate during exercise. Uncontrolled and not easily explained spontaneous variations occurred in the former instances, whereas they were relatively rare in the latter.

Since the pulse rate during exercise seemed to be such a reliable index of the oxygen consumption in the same person, we should expect the pulse rate to remain at a constant level during the exercise, just as the level of oxygen consumption remained fixed, the patient being in a "steady state." It was found that the pulse rate was, in fact, constant during the hour of exercise. However, Bowen<sup>11</sup> reported that there is, at the beginning of exercise, a sudden increase in pulse rate followed by a more gradual secondary rise, continuing to the end. Gillespie, Gibson and Murray<sup>12</sup> agreed with Bowen, but added that the pulse rate gradually increases "except possibly during the lightest work." Gillespie, Gibson and Murray also found that because of the tendency of the pulse rate to rise during exercise, the influence of successive increments of load on the pulse was not clearly distinguishable. Under the conditions of our experiment, however, successive increments of load, even relatively slight, were accompanied by a distinct increase in pulse rate. Thus, in table 3, it is seen that the pulse rate at an oxygen consumption of about 780 cc. was constant during the hour. In another experimental period with the rate of pedaling constant and the load increased from 4 to 5½ pounds (1,814.31 to 2,494.75 Gm.), the pulse rate increased from 93 to 102, corresponding in this case to an increase in oxygen consumption from 620 to 740 cc. per minute. The pulse rate then decreased from 102 to 94 per minute when the load was decreased from

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11 Bowen, W. P. Changes in Heart Rate, Blood Pressure and Duration of Systole Resulting from Bicycling, *Am J Physiol* **11** 59, 1904.

12 Gillespie, R. D., Gibson, C. R., Jr., and Murray, D. S. Effect of Exercise on Pulse Rate and Blood Pressure, *Heart* **12** 1, 1925.

5½ to 4 pounds There was a corresponding fall in oxygen consumption from 740 to 615 cc per minute

The relationship of oxygen consumption to pulse rate in the same person was not the same when the differences in oxygen consumption were due to differences in load as when they were due to training effect Thus, whereas a decrease of 125 cc in oxygen consumption due to a decrease in load was accompanied by a decrease of 8 in pulse rate (J L, table 3), a decrease of 140 cc in oxygen consumption due to a training effect was accompanied by a proportionately greater decrease, 16, in the pulse rate (J L, fig 8) The oxygen consumption in the two instances was in the same general range

*Mechanical Efficiency*—The changes in net mechanical efficiency corresponded grossly to the changes in oxygen consumption during work, as shown in the various figures Thus, in the case of C P (fig

TABLE 3—*Vital Capacity in the Course of Training in Two Patients with Rheumatic Mitral Stenosis and Aortic Insufficiency, and One Normal Subject*

Date	Time of Exercise, Minutes	Pulse Rate per Minute	Oxygen Consumption, Cc per Minute	Work, Kg Meters per Minute
1/12/33	7 10	112	770	255
	27 30	111	785	255
	57 60	111	785	255
3/ 3/33	7 10	93	620	175
	11			240
	19 22	102	740	240
	23			175
	31 34	94	615	175

4), there was an increase in net efficiency from 14.9 to 26.6 per cent In the normal subject, in whom the decrease in oxygen consumption during work was considerably less (fig 1), the increase in net efficiency was from 22.6 to 26 per cent

*Lactic Acid*—In one normal subject (E F, fig 3) and one patient (J L, fig 6) venous blood was taken in the ninth minute of the heavier exercise for the estimation of lactic acid In the normal subject, the lactic acid content gradually decreased with training from 39 to 28 mg per hundred cubic centimeters In the patient with rheumatic mitral and aortic disease, the lactic acid content of the blood during the exercise gradually decreased over a period of nine weeks from 38 to 13 mg The last figure represents practically the resting value, and indicates that after nine weeks a true "steady state" had been reached by this patient even for the heavier work (oxygen consumption, 1,100 to 1,200 cc) Bock, Dill and Edwards<sup>13</sup> found that work of this severity (moderate physical

13 Bock, A V, Dill, D B, and Edwards, H T Lactic Acid in Blood of Resting Man, J Clin Investigation 11:775, 1932



exercise) for thirty minutes was accompanied by no increase in the lactic acid in the venous blood. In the light of their results, our findings are to be interpreted to indicate that in the tenth minute of the work in our normal subjects, removal or resynthesis of lactic acid was still not keeping pace with its production. In the case of the last patient referred to, however, after nine weeks of training, and at a time when the patient was training for two hours daily with the work under consideration, the lactic acid level had reached a resting level in the tenth minute.

*Blood Pressure*—In exercise of the severity which we were studying a definite elevation of blood pressure occurs usually only in the systolic phase<sup>14</sup>. Therefore, it is to be expected that the lowering of the blood pressure during exercise which takes place in the course of training should be a lowering, essentially, of the systolic pressure. This is clearly shown in figure 4 (C P). The blood pressure at the beginning of training was 130 systolic and 78 diastolic during exercise, at the end of thirty-one days it was 110 systolic and 74 diastolic during exercise. There was a drop in systolic pressure of 20 mm. of mercury, while the diastolic pressure remained practically unchanged. Similar changes occurred in the other patients who showed a good response to training. In patients who showed no training effect, no significant changes were observed in either systolic or diastolic blood pressure.

#### COMMENT

In determining the significance of the changes observed in the resting state during a period of training, especially in dealing with patients with heart disease, it is important to know whether the patient during the period of observation is engaging in more or less activity than usual. Since the patients were in a ward during a large part of the day, their total activity was not great. However, the total physical activity of only two of the patients was less than usual while they were under observation. The activity of the other four patients was severely limited before we began our studies, more through fear and overcautiousness on their part than because of extreme restriction on the part of their physicians. In these two groups, the previous mode of life seemed not to play as important a rôle as might be expected. Of course, none of the patients was previously trained to ride a bicycle, so that regardless of the state of physical development and previous exercise a new type of work was being performed by all of them, and groups of muscles

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<sup>14</sup> (a) Bock, A. V., Vancaulaert, C., Dill, D. B., Folling, A., and Hurxthal, L. M. Studies in Muscular Activity. III. Dynamic Changes Occurring in Men at Work, *J. Physiol.* **66** 136, 1928. (b) Bansi, H. W., and Groscurth, G. Funktionsprüfung des Kreislaufs durch Messung der Herzarbeit, *Klin. Wchnschr.* **9** 1902, 1930. (c) Proger, S. H., and Dennig, H. A Study of the Circulation in Obesity, *I. Clin. Investigation* **11** 789, 1932.

were used in a manner hitherto not employed in daily activities. Hyde, Root and Curl<sup>15</sup> showed that the training effect observed in trained and untrained subjects is not essentially different when each performs a work to which he is not accustomed, in their study, pulling on an ergometer. In any event, the changes reported in the resting state may be taken as changes which occur in patients with rheumatic heart disease during a period of several weeks of moderate physical activity.

The changes in cardiac output which occurred in the one patient who responded so poorly to exercise are of interest. It will be recalled that the drop in cardiac output, associated with hemoptysis and diminished vital capacity, took place largely through an increase in the arteriovenous oxygen difference. It has been suggested before that one of the reserve mechanisms which the cardiovascular apparatus employs when the heart itself tends to become incompetent is an increase in the arteriovenous oxygen difference<sup>16</sup>. This is borne out by the fact that the cardiac output at rest in patients with varying degrees of heart failure is relatively low,<sup>17</sup> while the oxygen consumption or basal metabolism, except in patients with advanced heart failure, is practically unchanged<sup>18</sup>. The change in cardiac output is associated with an increase in oxygen utilization in the tissues, with a subsequent increase in the arteriovenous oxygen difference.

In the patient referred to, it is conceivable that because of pulmonary congestion there was a considerable increase in the length of time necessary for rebreathing, in order to obtain a true alveolar sample. In such a case, a high incorrect figure would be obtained for the arteriovenous oxygen difference, since the samples were taken at the usual times (eighteen and twenty-three seconds). The objection might also be made that the pulmonary congestion might even make it impossible to obtain true alveolar air samples. However, on the basis of the work of Grollman, Proger and Dennig,<sup>19</sup> the degree of pulmonary congestion in this case was not so great as to make such objections tenable.

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15 Hyde, I. H., Root, C. B., and Curl, H. A Comparison of the Effects of Breakfast, of no Breakfast and of Caffeine on Work in an Athlete and a Non-Athlete, *Am J Physiol* **43** 371, 1917.

16 Dennig, H., and Proger, S. H. Herzkrankte bei Arbeit, *Deutsches Arch f klin Med* **175** 170, 1933.

17 Kroetz, C. Messung des Kreislaufminutenvolumens mit Acetylen als Fremdgas. Ihre bisherigen Ergebnisse bei arteriellem Hochdruck und bei Dekompensation des Kreislauf, *Klin Wchnschr* **9** 966, 1930.

18 Du Bois, E. F. Basal Metabolism in Health and Disease, ed 2, Philadelphia, Lea & Febiger, 1927, p 364.

19 Grollman, A., Proger, S. H., and Dennig, H. Zur Bestimmung des Minutenvolumens mit der Azetylenmethode bei Arbeit, bei normalen und kranken Menschen, *Arch f exper Path u Pharmakol* **162** 463, 1931.

In the normal persons no change was observed in the vital capacity. There is very little convincing evidence that training involving even severe exercise affects considerably the vital capacity in the normal person<sup>20</sup>. It is the impression of some<sup>21</sup> that training does increase the vital capacity of normal persons, since trained athletes frequently have a greater vital capacity than nonathletes. Such evidence is only indirect, and it is open to the criticism that greater vital capacity, among other things, may be an inherent property of a person which enables him to develop into a first class athlete, whereas the person with a lower vital capacity never becomes an athlete. The increase in vital capacity which was observed in some of the patients during the training is striking evidence that some real form of cardiovascular adjustment takes place, perhaps in much the same manner as when heart failure without clear evidence of pulmonary congestion is being overcome when marked increase in vital capacity is seen. These changes indicate also that in the patient with heart disease, even when there is no evidence of cardiac weakness, the vital capacity may be somewhat less than it would be under normal conditions. Just why only two of the patients who showed a definite improvement in ability to perform the work had an increase in vital capacity, while the others did not, we are unable to say.

In the evaluation of the results of training, it becomes necessary to attempt to determine how much, if any, of the change during exercise is due to actual changes within the skeletal muscles, heart and lungs, and how much is due simply to a better coordination of movements as the result of practice. Because the work is light, one might be inclined to assume that the changes are the result chiefly of a neuromuscular adjustment, and that the development of a more efficient response to work is the result simply of less awkwardness in its performance. Had the normal subjects and the patients with heart disease responded alike to the long repeated exercises, such a view would be justifiable. It is even probable that the slight changes observed in the normal subjects were due wholly to the development of better coordination of movements. But the changes which were observed, for example in the patient of figure 4, are of such magnitude as to imply some real changes within the cardiovascular apparatus itself. Just what these changes are it is difficult to

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20 White, S. A., and McGuire, P. F. Vital Capacity in a Citizens Military Training Camp, *Arch Int Med* **36** 355 (Sept.) 1925. Wachholder, K. Die Vitalkapazität als Mass der körperlichen Leistungsfähigkeit, *Klin Wchnschr* **7** 295, 1928.

21 Worringer. *Ztschr f d ges phys Therap* **31** 132, 1926. Godin, P. *Contrôle de l'éducation physique, la croissance pendant l'âge scolaire*, Paris, Norbert Maloine, 1913, p. 205. Bainbridge, F. A. *The Physiology of Muscular Exercise*, ed 3, rewritten by A. V. Bock and D. B. Dill, New York, Longmans, Green & Co., 1931, p. 182.

determine. Probably one significant change is the increase in the vital capacity of the lungs which was observed. The fact that there were such marked differences in responses in a group of similar patients would make it seem also that something more than a neuromuscular adjustment was involved. Also, because for many days after training was begun, when there was no longer awkwardness in the performance of work or anxiety, significant changes continued to occur, one would be inclined to believe that actual physicochemical changes within the heart and skeletal muscles were taking place.

Gemmell, Booth and Pocock<sup>10</sup> concluded from their study of three normal persons that training to light muscular work brings about an increase in the efficiency of the cardiac and respiratory mechanisms rather than a change in the efficiency of the muscles. Such a change might be brought about, they thought, by changes in the oxidative mechanism of the cells, as suggested by Hill and Lupton<sup>22</sup> and Bock and his associates,<sup>141</sup> by an increase in the effective surface of the capillary bed supplying the muscles, or by changes in the nervous control of respiration and circulation during work.

The reason for the differences in response to training in the various patients is not clear. On the basis of the information at hand, it is not possible to predict what type of patient would and what type of patient would not show improvement with light exercise. That some do and some do not is obvious from the results. Perhaps it is significant that of the five patients studied who had regular rhythm, the three who showed a distinctly good training effect had disease of both the mitral and the aortic valves, whereas the two patients who showed no training effect (one of these had to stop the exercise because of a hemoptysis) had disease of the mitral valve alone. It might be thought that the changes which occur during training, whatever they are, are dependent on an adjustment between the greater and lesser circulations which can take place in the patient with a balanced disturbance, as it were, in both valves, whereas it cannot take place in a patient with the imbalance resulting from disease only of the mitral valve. This is simply a theoretical assumption and perhaps unjustified because of the small number of patients which we have studied, but it is consistent with the clinical observation that patients with mitral disease alone sometimes seem better when aortic insufficiency develops in addition.

One phase of the results in the patient the observations on whom are represented in figure 6 deserves special comment. We refer to the general increase in the values, which began after a distinct training effect had already occurred, that is, on the twenty-second day. There was an

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22 Hill, A. V., and Lupton, H. Muscular Exercise, Lactic Acid and Supply and Utilization of Oxygen, *Quart J Med* **16** 135, 1923.

unexplained loss of efficiency over a period of several days, during which time repeated observations were being made. There was, during this period, no evidence of infection, rheumatic or otherwise, nor were there subjective changes. Before this stage, the patient had obviously already reached what appeared to be the "trained" state for that particular exercise, so that the changes cannot be associated with possible differences in muscular coordination or skill in the performance of the work. There was no reason for the patient to become more awkward. It was thought that perhaps this phase represented very early evidence of heart failure, although the usual factors ordinarily associated with early failure of either the left or the right side of the heart were not manifested. Thus, there were no increasing shortness of breath, no tachycardia, no diminished vital capacity or breath-holding capacity, no cough and no increase in the intensity of the second sound over the pulmonic area. However, the increasing inefficiency was definite, although after a few days there was a return to the level of the "trained" state. Because of the possibility that early heart failure might occur in steplike fashion in a manner somewhat similar to late heart failure when there is usually more than one "break in compensation" before the end, exercise was continued for about eighty days after this unusual phase. A similar decrease in efficiency was not noted. The earlier reaction remains simply an interesting but unexplained phenomenon.

As early as 1915, Boothby<sup>23</sup> observed that "in the main, the pulse rate increases with oxygen consumption" in the human being. The results in these patients indicate that not only does the pulse rate vary directly with varying consumption of oxygen associated with different grades of work, but that the parallelism exists also when the consumption changes with the same work as in training. Because of this fact, the pulse rate during exercise served as a fairly accurate index of the mechanical efficiency. As the mechanical efficiency increased, the pulse rate during exercise became lower, and vice versa. Excitement was, of course, not present as a disturbing factor because of the continued repetition of the periods of exercise. As a result of these observations, it appears that measuring the pulse rate during exercise in patients with heart disease may serve as a helpful functional test. Assuming that the gross mechanical efficiency diminished with increasing cardiac weakness, we should expect to be able to detect such a state in a single person if his pulse rate were measured during the same exercise on different days. While differences in pulse rates in different persons are of no value, differences occurring in the same person would seem to be of real value as a guide to the physical state of a patient, and thus, perhaps, to the

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<sup>23</sup> Boothby, W. M. A Determination of the Circulation Rate in Man at Rest and at Work, *Am J Physiol* **37** 383, 1915

functional state of his cardiovascular apparatus. This does not apply to all types of heart disease, for observations which we have made on some patients with angina pectoris, even of the advanced type, indicate that frequently the pulse rate responds unusually slowly to exercise in this condition<sup>24</sup>

The pulse rate during exercise was found to be considerably more constant than the rate either at rest or after exercise. Spontaneous unexplained fluctuations not infrequently occurred under the latter circumstances. The length of time necessary for the pulse rate, after exercise, to return to the resting level was also not constant enough in our experiments to be of great aid as a guide to the efficiency with which the work was performed.

#### SUMMARY

1 Six patients with rheumatic heart disease pedaled on a stationary bicycle for from one to two hours daily for a period of from five to six weeks. Two normal persons in the same age group served as controls.

2 There were essentially no changes at rest in the pulse rate, respiratory rate (except for slowing in one case), pulmonary ventilation and oxygen consumption.

3 In one patient in whom exercise had to be discontinued because of the development of hemoptysis, the arteriovenous oxygen difference at rest showed an increase, and the cardiac output a decrease, just before and after the hemoptysis. These values returned to normal within a few days after the exercise was discontinued. In the other patients, the arteriovenous oxygen difference and cardiac output at rest were unchanged.

4 In the patients who improved with exercise, there was a slight slowing of the velocity of blood flow at rest.

5 The vital capacity in two of the patients who improved with exercise showed a definite increase. In the normal subjects, as well as in the other patients, it remained unchanged. Breath-holding ability generally paralleled the vital capacity.

6 Of the three patients who showed definite improvement in their response to exercise, there was an increase in the height of  $P_2$  in the electrocardiogram in one, and in the others an increase in the height of the T waves. In the patient in whom hemoptysis developed there was a slight prolongation of the P-R interval, an increase in the height of  $P_2$  and an inversion of  $P_3$ .

7 There were no definite changes in the teleoroentgenograms.

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<sup>24</sup> Proger, S. H., Minnich, W. R., and Magendantz, H. Circulatory Response to Exercise in Patients with Angina Pectoris, *Am. Heart J.*, to be published.

8 As determined by observations during exercise, the two normal subjects showed slight improvement, three patients with disease of both aortic and mitral valves showed marked improvement, one patient with only mitral disease showed no change, while another grew worse, and the only patient with an irregular heart beat (auricular fibrillation) who also had mitral stenosis and insufficiency showed a very slight improvement

9 A possible explanation for the varying responses is suggested

10 In one patient, after improvement had taken place, an unexplained relapse occurred which was overcome in a few days. In the same patient a mild infection with fever caused no change in his response to exercise immediately before and after the febrile state

11 A striking parallelism is shown to exist between the pulse rate and oxygen consumption during exercise through the period of training

# COPPER AND IRON IN HUMAN BLOOD

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## I NORMAL MEN AND WOMEN

The biologic importance of copper was brought to light by Bucholz and Meissner<sup>1</sup> in 1816, when they identified this element in plant life. Deverzie and Orfila,<sup>2</sup> in 1840, described the presence of copper in animal tissue. It was later recognized that all plant and animal tissue contains traces of copper. However, these traces were believed to be accidental, and no definite function was assigned to the element. Toward the latter part of the nineteenth century, copper was found in the blood of some marine animals.<sup>3</sup> Porter<sup>4</sup> reported appreciable amounts of copper in human blood in 1875.

## BIOLOGIC FUNCTIONS OF COPPER

The function of copper in the biologic organism has, as a result of recent experimentation, become more clearly defined. Copper acts chiefly as a catalyst with reference to (1) growth, (2) respiration and (3) hematopoiesis.

*Growth*—The earliest function assigned to copper was that of a promoter of growth. This function was inferred from the fact that the element was found in greatest abundance in the most actively growing parts of plants.<sup>5</sup> Later experiments proved that copper was actually

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1 Bucholz, C F, and Meissner, W, cited by Elvehjem, C A, and Lindow, C W. The Determination of Copper in Biological Materials, *J Biol Chem* **81** 435 (Feb) 1929.

2 Deverzie and Orfila, cited by Herkel, W. Ueber die Bedeutung des Kupfers in der Biologie und Pathologie, *Beitr z path Anat u z allg Path* **85** 513 (Nov) 1930.

3 Church, A M. Researches on Turacin, an Animal Pigment Containing Copper, *Phil Tr London* **159** 627, 1869, continued, *Proc Roy Soc London* **51** 399, 1892.

4 Porter, J A. Principles of Chemistry, improved edition, New York, Barnes, 1875, p 333.

5 Maquenne, L, and Demmousse, E. Sur la distillation et la migration du cuivre dans les tissus des plantes vertes, *Compt rend Acad d sc* **170** 87, 1920.



able to increase the growth of plants<sup>6</sup> Too concentrated a dose, however, inhibited growth The presence of copper in instances of rapid growth has been confirmed for animals also Rats maintained on a diet rich in copper showed a greater increase in weight than litter mates maintained on a diet restricted in copper<sup>7</sup> In almost all lower animals the liver of the embryo and of the new-born contains a higher percentage of copper than for that of the adult of the same species<sup>8</sup> In man the liver of the fetus also shows a higher percentage of copper than does the adult liver<sup>9</sup> Such relative increase may represent the need for copper during the period of rapid growth Most investigators prefer, however, to regard the excessive storage of copper and iron in the fetal liver as necessary to supplement the potential anemia-producing diet on which the infant is to subsist in the first year of extra-uterine life

*Respiration*—Copper plays an important rôle in the respiratory process of certain crustaceans and mollusks In hematocyanine,<sup>10</sup> the respiratory pigment found in the colorless and blue blood of these marine animals, copper assumes the function that iron performs in the hemoglobin of warm-blooded animals Aside from this outstanding instance of the ability of copper to act as a respiratory catalyst, the conclusions reached in other investigations on the relationship of copper to respiration are in a confused state The confusion arises from a failure to distinguish the toxic property of copper from its stimulating or catalyzing ability The beneficial influence of minute quantities of copper is rapidly converted into a malignant oligodynamic factor as the concentration in a given medium goes up Although known to depress the respiration of yeasts and other lower forms, copper in physiologic concentration acts as a stimulant Flinn and Inouye<sup>7</sup> found that copper increases the oxygen-combining capacity of the blood, while Guillemet<sup>11</sup> traced in animals a proportionality between the respiratory capacity and the copper content of the blood

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6 Allison, R N , Bryan, O C , and Hunter, J H Florida Agric Exper Sta Bull , 190, 1927

7 Flinn, F B , and Inouye, J M Some Physiological Aspects of Copper in the Organism, J Biol Chem **84** 101 (Oct ) 1929

8 Cunningham, I J Some Biochemical and Physiological Aspects of Copper in Animal Nutrition, Biochem J **25** 1267, 1931

9 Morrison, D B , and Nash, T P , Jr The Copper Content of Infant Livers, J Biol Chem **88** 479 (Sept ) 1930

10 Fredericq, L Sur l'organisation et la physiologie du poulpe, Bull Acad roy de med de Belgique **46** 710, 1878

11 Guillemet, R L'abaissement du taux du cuivre total du sang au cours de l'anémie expérimentale par saignées chez le chien, Compt rend Soc de biol **109** 221 (Jan ) 1932

Copper markedly accelerates the spontaneous oxidation of iron *in vitro*. Quartaroli,<sup>12</sup> who made a thorough analysis of the relationship of copper to iron, observed this acceleration even in the presence of minute traces of copper. He was inclined to believe that the importance of iron in the organism as a respiratory ferment or inductor of oxidation in the tissues is chiefly dependent on its co-activation with copper. Furthermore, the oxidation of glutathione is accomplished by the action of copper as a catalyst, whereas iron and other metals fail in this capacity.<sup>13</sup> The importance of copper increases by virtue of this physiologic relationship to the inductors of oxidation and reduction processes in the body.

*Hematopoiesis*—McHargue, Healy and Hill<sup>14</sup> drew attention to the importance of copper in the formation of hemoglobin and in the metabolism of animals having red blood cells. It was the intensive work, however, of Waddell, Steenbock, Elvehjem and Hart<sup>15</sup> which established copper as an essential factor in hematopoiesis. Their work has now been confirmed in many laboratories.

The mechanism by which copper catalyzes the formation of hemoglobin is not clear. Elvehjem's<sup>16</sup> experiments on yeast show that copper stimulates the formation of an iron complex,  $\alpha$ -cytochrome. Since this pigment is related to the hemochromogens, which are derivatives of hemoglobin, the relationship of copper to the production of hemoglobin may depend in the animal organism on a similar activity of copper. Hill<sup>17</sup> has demonstrated that the administration of copper to animals results in a reduction in the amount of inorganic iron stored in the liver and in a corresponding increase in the organic form. The organic form of iron, he suggested, is the precursor of hemoglobin. Working on this suggestion, Cunningham<sup>8</sup> postulated a copper porphyrin which is converted into an iron porphyrin as the iron replaces the copper to form the hemoglobin molecule. Apparently copper is active in effecting the conversion of stored iron into the hemoglobinous

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12 Quartaroli, A. Il binomio ferro-rame in chimica e in biologia, *Ann di chim applic* **22** 517, 1932.

13 Voegtlin, C., Johnson, J. M., and Rosenthal, S. M. Catalytic Action of Copper in Oxidation of Crystalline Glutathione, *Pub Health Rep* **46** 2234 (Sept 18) 1931.

14 McHargue, J. S., Healy, D. J., and Hill, E. S. Relation of Copper to Hemoglobin Content of Rat Blood, *J Biol Chem* **78** 637 (Aug.) 1928.

15 Waddell, J., Steenbock, H., Elvehjem, C. A., and Hart, E. B. Iron in Nutrition. Further Proof that Anemia Produced on Diets of Whole Milk and Iron is Due to Deficiency in Copper, *J Biol Chem* **83** 251 (July) 1929.

16 Elvehjem, C. A. Rôle of Iron and Copper in Growth and Metabolism of Yeast, *J Biol Chem* **90** 111 (April) 1931.

17 Hill, R. Method for Estimation of Iron in Biological Material, *Proc Roy Soc., London, s B* **107** 205 (Nov.) 1930.

form. In performing this function, copper tends to reduce the amount of iron stored in the reservoirs of the body. The work of Josephs<sup>18</sup> and of Elvehjem and Sherman<sup>19</sup> points to such a conclusion. On the other hand, this view was contested by Kletzein, Buchwald and Hudson,<sup>20</sup> who maintained that copper induces the retention of iron in the body. For several years Mallory<sup>21</sup> championed the latter contention in its application to the pathologic findings in hemochromatosis. These authors maintained that copper is the etiologic factor in this disease and, more specifically, that it is responsible for the deposits of hemosiderin granules containing iron in the body tissues. Reports from other laboratories are not in agreement with these findings.

It is widely accepted that copper in the presence of iron stimulates the regeneration of hemoglobin in animals made anemic by a milk diet. In addition, copper alone is also known to catalyze the formation of red cells.<sup>22</sup> Thus, animals receiving copper unsupplemented by iron show an increased erythrocyte level despite the low percentage of hemoglobin which persists. In the milk anemia, therefore, there is a specific deficiency of copper which must be corrected before the utilization of iron for the production of hemoglobin and before the formation of erythrocytes. It thus assumes a place in the list of deficiency anemias which occupy a prominent place in the recent literature. Already, attention is being focused on liver, iron, thyroxine, vitamin B<sub>2</sub>, vitamin C and other substances the absence of any one of which results in a particular type of anemia. Clinicians have been reluctant, however, to accept copper as a specific therapeutic agent.

If anemia caused by a deficiency of copper exists, it seems logical to expect such a deficiency to be reflected in the blood stream by a diminished copper content. We determined the copper content of the blood of normal men and women and of patients with various pathologic conditions in an effort to study the problem more fully.

#### COPPER IN THE BLOOD

The distribution of copper among the various components of the blood has been studied by several investigators. Elvehjem, Steenbock

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18 Josephs, W. H. Studies on Iron Metabolism and Influence of Copper, *J Biol Chem* **96** 599 (May) 1932.

19 Elvehjem, C. A., and Sherman, W. C. Action of Copper in Iron Metabolism, *J Biol Chem* **98** 309 (Oct) 1932.

20 Kletzein, S. W., Buchwald, K. W., and Hudson, L. Mineral Metabolism—Copper and Iron, *Proc Soc Exper Biol & Med* **30** 645 (Feb) 1933.

21 Mallory, F. B. Relation of Chronic Poisoning with Copper to Hemochromatosis, *Am J Path* **1** 117 (Jan) 1925.

22 Stein, H. B., and Lewis, E. C. Stimulating Action of Copper on Erythropoiesis, *J Nutrition* **6** 465 (Sept) 1933.

and Hart,<sup>23</sup> Sarata<sup>24</sup> and Quartaroli<sup>12</sup> have found most of the copper of the blood to be present in the erythrocytes. In various other investigations in which a comparison of the copper content of the erythrocytes and that of the serum was made, the serum was found to possess the greater share of the total quantity present in the whole blood.<sup>25</sup> Guillemet<sup>26</sup> reported that the serum possesses almost the entire copper content of the blood. Our determinations of the copper content of the plasma and of the erythrocytes of dog blood reveal an equal distribution of the copper content of the whole blood between them. An illustration is given below

	Copper, Mg
10 cc of whole blood	0.0091
Erythrocytes from 10 cc of blood	0.0043
Plasma from 10 cc of blood	0.0046
10 cc of plasma	0.0099

Because of the differences reported in the copper content of the components of the blood, we feel justified in assuming that a reliable determination of the copper content of the blood can be made only on the whole blood.

*Determination of Copper*—The modern trend in quantitative chemical examination of the blood is to employ a micro-method which is based on colorimetry. The colorimetric estimation of the copper content of the blood is made difficult by the presence of substances in the blood which interfere with the color produced by copper reagents. Iron, which is from three hundred to five hundred times more abundant than copper in the blood, is the chief offender. The use by other investigators of the blood serum instead of the whole blood has probably been an attempt to avoid the error introduced by the interfering iron.

Although many methods are available for the determination of copper in organic material, few are practicable for measuring accurately the minute quantities present in the blood. The ideal method should make possible the complete extraction of the copper, to which a sensitive reagent could then be applied to give quantitative results. However, the complete extraction of copper with avoidance of the interference of other blood elements is a difficult task. We spent much time and labor in the construction and use of a piece of apparatus, recently

23 Elvehjem, C. A., Steenbock, H., and Hart, E. B. Is Copper a Constituent of the Hemoglobin Molecule? *J. Biol. Chem.* **83** 21 (July) 1929.

24 Sarata, U. Studies in the Biochemistry of Copper. II. The Copper Content of the Blood with a Method for Its Determination, *Jap. J. Med. Sci. Tr.*, II *Biochem.* **2** 261 (Oct.) 1933.

25 Schindel, L. Ueber den Kupfergehalt des Blutes, *Klin. Wchnschr.* **10** 743 (April 18) 1931.

26 Guillemet, R. Sur le cuivre sanguin, sa répartition entre les différents constituants du sang normal, *Compt. rend. Soc. de biol.* **109** 652 (March) 1932.

described,<sup>27</sup> for the micro-electric separation of copper from the blood ash. In our hands the very small quantities of metal present in a convenient sample of blood could not be plated out successfully. Sarata<sup>24</sup> and Elvehjem and Lindow<sup>28</sup> have also discarded the electrolytic method because of its limited applicability.

The copper reagent which has gained the greatest popularity is sodium diethyl-di-thiocarbamate, described by Callan and Henderson<sup>29</sup>. A golden yellow color is produced, even with very minute quantities of copper. Warburg<sup>30</sup> originally suggested the use of pyrophosphate, which combines with iron to form an inactive compound that does not interfere with the determination of copper in the blood. In the method reported by McFarlane,<sup>31</sup> both the carbamate reagent and pyrophosphate are used. We followed the technic of McFarlane for the determinations of copper on the blood of the fifty normal men listed in table 1. However, we found that the iron is not completely bound by the pyrophosphate, even when large quantities of the reagent are added. As a result of the presence of unbound iron, the final color produced is often tinged brown instead of pure golden yellow. This interfering color renders difficult the comparison with the standard and is also apt to give higher results. In all other determinations reported in this paper we used the iron precipitation method described below.

#### METHODS

The determinations of iron and copper reported in this paper were made during the months from January to December 1933. The normal male subjects were freshman medical students, from 20 to 25 years of age, who had recently been examined and found in good health. The normal female subjects were nurses from 20 to 30 years of age and in good health.

Special precautions were taken to obtain pure reagents, free from copper and iron. Acids, alkalis and water were redistilled from glass and were tested at frequent intervals for contamination.

Blood counts were made with standardized pipets and counting chambers on blood drawn by cutaneous puncture of the lobe of the ear. In cases of severe anemia the count was checked on the venous blood.

Seven cubic centimeters of blood was drawn from the vein into a wide-mouthed tube containing 0.02 Gm of sodium oxalate. The determinations on copper and iron were made shortly afterward.

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27 Clark, B. L., and Hermance, H. W. Improved Apparatus for Micro-Electroanalysis, *J. Am. Chem. Soc.* **54** 877 (March) 1932.

28 Elvehjem, C. A., and Lindow, C. W. Determination of Copper in Biochemical Materials, *J. Biol. Chem.* **81** 435 (Feb.) 1929.

29 Callan, T., and Henderson, J. A. R. New Reagent for Colorimetric Determination of Minute Amounts of Copper, *Analyst* **54** 650 (Nov.) 1929.

30 Warburg, O. Methode zur Bestimmung von Kupfer und Eisen und über den Kupfergehalt des Blutserums, *Biochem. Ztschr.* **187** 255, 1927.

31 McFarlane, W. D. Application of the Sodium Diethyldithiocarbamate Reaction to the Micro-Colorimetric Determination of Copper in Organic Substances, *Biochem. J.* **26** 1022, 1932.

The determinations of iron were made on 0.5 cc samples by a modified Wong method which we have already described<sup>32</sup>

The determinations of copper were made as follows. Five cubic centimeters of blood was pipetted into an acid-washed copper-free vitreosil dish and dried on a hot plate with constant stirring. The dish was transferred to an electric muffle and for eight hours ashed at a low temperature. After cooling, the ash was moistened with 1 cc of concentrated nitric acid and replaced on the hot plate to evaporate the excess acid. The ash was dissolved in 3 cc of six times normal hydrochloric acid and was transferred quantitatively to a 15 cc centrifuge tube. Two cubic centimeters of ammonia water containing 28 per cent of gaseous ammonia was pipetted into the tube, and the mixture was stirred until the gelatinous ferric hydroxide precipitate appeared throughout. The tube was then centrifugated at 1,500 revolutions per minute for twenty minutes.

The supernatant clear fluid was carefully poured off into a 25 cc glass-stoppered cylinder, and the precipitate at the bottom of the centrifuge tube was redissolved by the addition of 0.8 cc of six times normal hydrochloric acid. Five cubic centimeters of distilled water was used to wash down the sides of the tube in order to dilute the acid solution. The ferric hydroxide was reprecipitated by adding 0.5 cc of ammonia water, and the tube was centrifugated for another twenty minutes. The clear supernatant fluid was combined with the first sample in the glass cylinder. Two cubic centimeters of a 0.5 per cent aqueous solution of the carbamate reagent was added, after which 4 cc of amyl alcohol was accurately measured into each cylinder. The colored layer of alcohol was removed by means of a pipet and filtered into a microcup through an acid-washed 1 inch (2.5 cm) filter paper. The filter paper removed the excess water.

A comparison was made with a standard solution containing 0.01 mg of copper to which had been added the same quantities of each of the reagents as were added to the unknown sample. A blank was run with each series of determinations.

#### EXPERIMENTAL DATA ON IRON IN HUMAN BLOOD

*Normal Iron Content*—The average iron content of the whole blood for the series of one hundred normal men listed in tables 1 and 2 was 50.25 mg per hundred cubic centimeters of blood. The figure is in close agreement with the amount (50.01 mg) which we reported for another series of one hundred normal men. The final average iron content based on determinations on blood from two hundred normal men was  $50.13 \pm 0.15$  mg<sup>33</sup> per hundred cubic centimeters.

The blood of fifty normal women, listed in table 3, averaged 44.11 mg of iron per hundred cubic centimeters. This was slightly higher than the average figure (42.67 mg) obtained in our previous series of fifty normal women. The final average iron content of the blood of one hundred normal women was  $43.42 \pm 0.19$  mg per hundred cubic centimeters.

32 Sachs, A., Levine, V. E., and Appelsis, A. Iron in Human Blood, Arch Int Med **52** 366 (Sept.) 1933.

33 This is the probable error of distribution. Thus, there is a fifty-fifty chance that the iron content of normal whole blood will fall somewhere within the range between average plus probable error and average minus probable error.

TABLE 1—*Values for Copper and Iron in the Blood of Fifty Normal Men Aged 20 to 25\**

Name	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
1 Gre	4,288,000	0 146	50 00	14 93	11 66	1 17
2 Del	4,864,000	0 155	49 00	14 63	10 07	1 01
3 McG	4,512,000	0 137	47 25	14 10	10 47	1 05
4 Lan	4,832,000	0 123	48 55	14 49	10 05	1 00
5 Roc	5,088,000	0 130	46 30	13 82	9 10	0 91
6 Bur	4,960,000	0 153	46 55	13 90	9 39	0 94
7 Kab	4,576,000	0 132	51 35	15 33	11 22	1 12
8 McL	4,992,000	0 123	54 30	16 21	10 88	1 09
9 Mad	4,736,000	0 127	49 35	14 73	10 42	1 04
10 Ran	5,120,000	0 133	52 10	15 55	10 18	1 02
11 Whe	5,184,000	0 135	55 35	16 67	10 77	1 03
12 Lov	4,480,000	0 138	51 30	15 31	11 45	1 15
13 Jan	4,704,000	0 103	45 45	13 57	9 66	0 97
14 Kan	4,768,000	0 138	50 00	14 93	10 49	1 05
15 McC	4,736,000	0 138	50 00	14 93	10 56	1 06
16 O'Fa	4,480,000	0 133	47 85	14 28	10 68	1 07
17 O'Co	4,256,000	0 135	50 85	15 18	11 95	1 20
18 Vit	4,800,000	0 133	50 55	15 09	10 53	1 05
19 Pis	4,544,000	0 138	48 35	14 43	10 64	1 06
20 Wat	4,256,000	0 155	46 55	13 90	10 94	1 09
21 Fro	4,512,000	0 146	52 10	15 55	11 55	1 16
22 Pav	4,384,000	0 150	48 10	14 36	10 97	1 10
23 Dic	4,704,000	0 135	50 50	15 08	10 74	1 07
24 Dol	4,448,000	0 156	47 35	14 13	10 65	1 06
25 Cur	4,160,000	0 149	49 20	14 69	11 83	1 18
26 Var	4,896,000	0 156	53 20	15 83	10 87	1 09
27 Sil	4,960,000	0 160	51 30	15 31	10 34	1 03
28 Sod	4,576,000	0 135	54 65	16 31	11 94	1 19
29 Sem	5,056,000	0 121	51 30	15 46	10 25	1 02
30 San	4,672,000	0 149	53 20	15 88	11 39	1 14
31 Kar	5,024,000	0 138	50 00	14 93	9 95	1 00
32 Fra	4,928,000	0 150	54 45	16 25	11 05	1 10
33 Sul	4,672,000	0 144	50 65	15 12	10 84	1 08
34 Tol	4,832,000	0 154	50 45	15 06	10 44	1 04
35 Tuv	5,280,000	0 142	48 30	14 42	9 15	0 92
36 Ell	4,992,000	0 148	54 00	16 12	10 82	1 08
37 McF	5,152,000	0 156	50 00	14 93	9 70	0 97
38 Ant	4,998,000	0 137	50 20	14 99	10 04	1 00
39 Wei	4,448,000	0 120	48 65	14 52	10 94	1 09
40 Mar	4,448,000	0 140	46 50	13 83	10 45	1 05
41 Mar	4,800,000	0 136	49 20	14 69	10 25	1 03
42 Man	4,160,000	0 134	50 50	15 07	12 14	1 21
43 McC	4,192,000	0 110	48 55	14 49	11 58	1 16
44 Bum	4,832,000	0 146	50 00	14 93	10 35	1 04
45 Gra	4,480,000	0 137	52 65	15 72	11 75	1 18
46 Num	4,768,000	0 147	53 20	15 83	11 16	1 12
47 Bri	4,448,000	0 160	50 20	14 99	11 29	1 13
48 Suz	4,256,000	0 133	50 10	14 96	11 77	1 18
49 Thu	4,224,000	0 121	51 30	15 31	12 14	1 21
50 Fle	4,576,000	0 141	52 90	15 79	11 56	1 16
Average	4,681,000	0 141	50 29	15 01	10 78	1 08

\* The values in the last three columns of this and the following tables (unless otherwise indicated) were determined by means of the following equations

$$\text{Hemoglobin} = \frac{\text{milligrams of iron in 100 cc of blood}}{3.35} = \text{grams of hemoglobin in 100 cc of blood}$$

$$\text{Iron index} = \frac{\text{milligrams of iron in 100 cc of blood}}{\text{first three figures of red blood cell count}}$$

$$\text{Iron color index} = \frac{\text{percentage of iron}}{\text{percentage of red blood cells}}, \text{ when } \begin{cases} 50 \text{ mg of iron} = 100 \text{ per cent} \\ 5,000,000 \text{ red blood cells} = 100 \text{ per cent} \end{cases}$$

$$\text{therefore} = \frac{\text{milligrams of iron in 100 cc of blood}}{\text{first two figures of red blood cell count}}$$

Helmer and Emerson,<sup>34</sup> using the same method, recently corroborated our results for the iron content of the whole blood of normal men. Their figure for the iron content of the whole blood of normal women, however, more nearly conforms with the average (44.11 mg) of the

TABLE 2—*Values for Copper and Iron in the Blood of Fifty Normal Men, Aged 20 to 25*

Name	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
1 And	5,152,000	0.133	50.00	14.93	9.71	0.97
2 Bar	4,928,000	0.134	50.00	14.93	10.15	1.01
3 Ben	4,576,000	0.130	50.50	15.07	11.04	1.10
4 Bla	4,640,000	0.125	51.00	15.22	10.99	1.10
5 Blo	4,800,000	0.129	55.55	16.58	11.57	1.16
6 Bro	4,704,000	0.124	49.00	14.63	10.42	1.04
7 Cam	4,544,000	0.134	53.20	15.88	11.71	1.17
8 Can	4,896,000	0.143	49.50	14.78	10.11	1.01
9 Chr	4,860,000	0.132	47.35	14.13	9.74	0.97
10 Coy	4,544,000	0.145	53.20	15.88	11.71	1.17
11 Col	4,672,000	0.152	47.60	14.21	10.19	1.02
12 Die	5,184,000	0.130	52.35	15.63	10.10	1.01
13 Cro	4,896,000	0.140	49.00	14.63	10.01	1.00
14 Dav	4,768,000	0.140	48.30	14.42	10.13	1.01
15 Dav	4,832,000	0.136	51.00	15.22	10.55	1.06
16 Doo	4,832,000	0.140	49.50	14.78	10.24	1.02
17 Dre	4,512,000	0.141	47.85	14.28	10.61	1.06
18 Far	4,512,000	0.133	46.10	13.76	10.22	1.02
19 Lck	4,432,000	0.125	54.05	16.13	12.20	1.02
20 Fau	5,120,000	0.131	50.00	14.93	9.77	0.98
21 Fis	4,864,000	0.127	45.85	13.69	9.43	0.94
22 Fav	4,480,000	0.126	46.10	13.76	10.29	1.03
23 Fra	4,224,000	0.142	47.60	14.21	11.27	1.13
24 Fox	4,416,000	0.132	51.30	15.31	11.62	1.16
25 Gio	4,448,000	0.128	54.95	16.40	12.35	1.24
26 Gla	4,480,000	0.130	50.50	15.07	11.27	1.13
27 Gia	4,480,000	0.125	51.00	15.22	11.38	1.14
28 Gre	4,736,000	0.132	48.90	14.60	10.32	1.03
29 Han	4,800,000	0.132	49.25	14.70	10.26	1.03
30 Har	4,768,000	0.135	51.00	15.22	10.70	1.07
31 Has	4,736,000	0.140	51.00	15.22	10.77	1.08
32 Jac	4,864,000	0.140	50.00	14.93	10.28	1.03
33 Irv	5,024,000	0.139	51.30	15.31	10.21	1.02
34 Hal	5,248,000	0.130	50.25	15.00	9.58	0.96
35 Het	4,544,000	0.127	50.00	14.93	11.00	1.10
36 Pet	4,318,000	0.133	50.00	14.93	11.53	1.16
37 Sma	4,736,000	0.133	47.85	14.28	10.10	1.01
38 Pos	4,608,000	0.126	51.00	15.22	11.07	1.11
39 Ric	5,248,000	0.129	51.55	15.39	9.82	0.98
40 Saw	4,736,000	0.141	47.60	14.21	10.05	1.01
41 Sac	4,160,000	0.143	47.60	14.21	11.44	1.14
42 Tur	5,120,000	0.139	52.65	15.72	10.03	1.00
43 Ste	4,352,000	0.111	48.05	14.34	11.04	1.10
44 Swa	4,544,000	0.120	51.55	15.39	11.34	1.13
45 McM	4,800,000	0.120	50.05	14.94	10.43	1.04
46 Wic	4,480,000	0.125	49.75	14.85	11.10	1.10
47 Mic	4,896,000	0.110	52.90	15.79	10.80	1.08
48 O'Ne	4,288,000	0.139	51.30	15.31	11.96	1.20
49 Pct	4,704,000	0.121	52.35	15.63	11.13	1.11
50 O'Sh	4,800,000	0.127	51.30	15.31	10.69	1.07
Average	4,706,000	0.132	50.19	14.98	10.69	1.07

present series (table 3) than with the 42.67 mg which was the average for the earlier group of fifty women. Nevertheless, we do not believe that the higher results obtained in our last series of fifty women should replace those previously reported as being more nearly correct. In our large series of tests of the blood of normal women the range was wider

34 Helmer, O. M., and Emerson, C. P., Jr. Iron Content of the Whole Blood of Normal Individuals, *J. Biol. Chem.* **104**: 157 (Jan) 1934.



TABLE 3—*Values for Copper and Iron in the Blood of Fifty Normal Women, Aged 20 to 30*

Name	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index*
1 Wur	4,288,000	0 147	44 85	13 39	10 46	1 05
2 Cop	4,672,000	0 137	44 20	13 19	9 46	0 95
3 Sue	5,344,000	0 157	44 10	13 16	8 25	0 83
4 Mey	5,142,000	0 113	45 60	13 61	8 87	0 89
5 Dul	4,488,000	0 120	44 65	13 33	9 95	0 99
6 Dra	4,896,000	0 134	42 00	12 54	8 58	0 86
7 Gla	5,408,000	0 118	47 60	14 21	8 80	0 88
8 Bro	4,124,000	0 141	38 90	11 61	9 43	0 94
9 Ful	4,384,000	0 131	40 00	11 94	9 12	0 91
10 Dee	5,056,000	0 160	43 10	12 87	8 52	0 85
11 Dah	4,464,000	0 124	43 85	13 09	9 82	0 98
12 Fol	4,768,000	0 136	45 05	13 45	9 45	0 95
13 Wil	4,832,000	0 128	46 50	13 88	9 62	0 96
14 Jan	4,960,000	0 142	41 30	12 33	8 33	0 83
15 Yos	4,320,000	0 137	39 85	11 89	9 22	0 92
16 Det	4,352,000	0 116	40 00	11 94	9 19	0 92
17 McK	5,112,000	0 120	46 70	13 94	9 14	0 91
18 Tom	4,960,000	0 140	46 30	13 82	9 34	0 93
19 Bux	4,000,000	0 143	46 30	13 82	11 58	1 16
20 Woc	4,204,000	0 129	44 85	13 39	10 67	1 07
21 Cla	4,544,000	0 124	46 70	13 94	10 23	1 03
22 Lis	4,420,000	0 120	45 45	13 57	10 28	1 03
23 And	4,512,000	0 128	43 30	12 93	9 59	0 96
24 Bye	4,288,000	0 123	41 85	12 49	9 76	0 98
25 Her	4,160,000	0 130	45 65	13 63	10 97	1 10
26 Ste	4,224,000	0 137	46 45	13 87	11 00	1 10
27 Lyo	4,416,000	0 133	45 45	13 57	10 29	1 03
28 Hug	4,160,000	0 133	39 85	11 90	9 58	0 96
29 Mil	4,224,000	0 137	46 10	13 76	10 91	1 09
30 All	4,320,000	0 121	43 10	12 87	9 98	1 00
31 Sta	4,288,000	0 118	41 15	12 28	9 60	0 96
32 Gle	4,544,000	0 122	45 05	13 45	9 91	0 99
33 Poh	4,352,000	0 145	46 00	13 73	10 57	1 06
34 Ken	4,950,000	0 126	45 05	13 45	9 10	0 91
35 Mey	4,460,000	0 130	45 45	13 57	10 19	1 02
36 Voi	4,410,000	0 144	42 75	12 76	9 69	0 97
37 Kel	5,000,000	0 127	46 10	13 76	9 22	0 92
38 Mei	3,875,000	0 137	40 65	12 13	10 49	1 05
39 Tho	4,620,000	0 128	46 50	13 88	10 07	1 01
40 McC	4,160,000	0 127	44 45	13 27	10 69	1 07
41 Lan	4,850,000	0 130	44 05	13 15	9 08	0 91
42 Bur	4,265,000	0 135	41 85	12 49	9 81	0 98
43 Hil	4,770,000	0 132	44 50	13 28	9 33	0 93
44 Bob	5,000,000	0 121	45 30	13 52	9 06	0 91
45 Bul	4,850,000	0 120	46 50	13 88	9 59	0 96
46 Kel	4,228,000	0 127	44 65	13 33	10 56	1 06
47 Jor	3,776,000	0 160	46 50	13 88	12 31	1 23
48 All	4,450,000	0 146	45 45	13 57	10 21	1 02
49 McC	4,950,000	0 121	46 95	14 01	9 49	0 95
50 Jos	4,000,000	0 112	39 50	11 79	9 88	0 99
Average	4,560,000	0 131	44 11	13 18	9 79	0 98

\* Iron color index =  $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}}$  when  $\left\{ \begin{array}{l} 45 \text{ mg of iron} = 100 \text{ per cent} \\ 4,500,000 \text{ red blood cells} = 100 \text{ per cent} \end{array} \right.$   
therefore =  $\frac{\text{milligrams of iron in 100 cc of blood}}{\text{first two figures of red blood cell count}}$

TABLE 4—*Values for Iron and Copper in the Blood of Normal Men and Women*

Group	Red Blood Cell Count	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
A 50 men	4,681,000	0 141*	50 29	15 01	10 78	1 08
B 50 men	4,706,000	0 132*	50 19	14 98	10 69	1 07
C 50 men	4,963,520		51 05	15 25	10 32	1 03
D 50 men	5,045,280		48 97	14 62	9 71	0 97
Average	4,879,160		50 13	14 96	10 37	1 04
F 50 women	4,560,000	0 131	44 16	13 18	9 79	0 98
F 50 women	4,457,000		42 67	12 74	9 59	1 01
Average	4,508,500		43 42	12 96	9 69	0 99

\* Different methods were used in estimating the copper content of groups A and B

and the variability was greater than that for normal men. We feel that this fluctuation in the iron content is the result of the instability of the female hematopoietic system. Such a view is in harmony with the findings of Bloomfield and Pollard<sup>35</sup>. In a comparison of the blood values of normal men and women, the latter showed a greater incidence of achlorhydria, which may account for the greater tendency toward the anemic state in women.

For clinical purposes, the mathematical index, the mode, which represents the figure that appears most frequently in a series and around which the majority of the figures are grouped, is a better guide than the average. The mode for the one hundred normal women was 45 mg of iron, while the mode for the two hundred normal men remained the same as the average, 50 mg.

*Hemoglobin*—Since the publication of our report on the iron content of human blood, several papers have appeared on the same subject<sup>36</sup>. These investigations confirm our conclusions that hemoglobinometers may be standardized by the use of the figures for the iron content of the blood. Using the factor<sup>37</sup>  $\text{hemoglobin} = \frac{\text{milligrams of iron in 100 cc of blood}}{3.35}$  the amount of hemoglobin in grams per hundred cubic centimeters of blood may be estimated from the iron content of the whole blood. Clinical hemoglobinometers have as their standard for 100 per cent figures which range from 13 to 17 Gm of hemoglobin per hundred cubic centimeters of blood. Our large series of figures for the blood iron of normal men and women is also of value in establishing normal standards for the hemoglobin content.

The average hemoglobin content for two hundred normal men was  $14.96 \pm 0.045$  Gm per hundred cubic centimeters of blood. The average hemoglobin for one hundred normal women was  $12.96 \pm 0.06$  Gm.

In the determination of the percentage of hemoglobin by most clinical methods one standard is employed for both men and women. It is obvious from the marked difference between the iron content of the blood of normal men and that of normal women that the percentage of hemoglobin for the two sexes is also widely separated. The corrected averages, the modes, which were 50 mg of iron per hundred cubic centimeters of blood for normal men and 45 mg for normal women, emphasize this difference.

35 Bloomfield, A. L., and Pollard, W. S. *Gastric Anacidity—Its Relation to Disease*, New York, The Macmillan Company, 1933.

36 Dowden, C. W., and McNeill, C. *Clinical Study of Blood Iron and Hemoglobin*, *J. Lab. & Clin. Med.* **19**:362 (Jan.) 1934. Haden, R. L. *Determination of Hemoglobin by the Iron Content Method*, *ibid.* **19**:406 (Jan.) 1934.

37 Butterfield, E. *Ueber die Lichtextinktion, das Gasbindungsvermogen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zustanden*, *Ztschr. f. physiol. Chem.* **62**:173, 1909.

The figure 50 mg for normal men lends itself admirably for clinical use. This represents 100 per cent of iron. Since the hemoglobin is a multiple of iron, one may state that 50 mg of iron corresponds to 100 per cent of hemoglobin. In general, then, the number of milligrams of iron per hundred cubic centimeters of blood of a man may be conveniently converted into the percentage of hemoglobin by multiplying by 2. If this formula is applied to the mode for women (45 mg of iron) the hemoglobin content of the average woman is only 90 per cent. Herein lies the disadvantage of the use of a single standard for the estimation of the hemoglobin content for both sexes. By its use the figure 80 per cent of hemoglobin would represent a similar level for both sexes, whereas it is obvious from our figures that such a concentration of hemoglobin would actually represent a more anemic level in a man than in a woman. If the scale of 100 per cent of hemoglobin is to be retained for both sexes the number of milligrams of iron per hundred cubic centimeters of blood for women must be multiplied by 2.22 to correspond with the number of milligrams of iron per hundred cubic centimeters of blood multiplied by 2 for men.

*Iron Color Index*—The iron index of Murphy, Lynch and Howard<sup>38</sup> is obtained as follows

$$\frac{\text{milligrams of iron in 100 cc of blood}}{\text{red blood cells in millions}} = \text{iron index}$$

We suggested<sup>32</sup> the iron color index,  $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}}$ , for use "in order to retain the convenient +1 and -1 of the older color index and yet take advantage of the greater accuracy of the iron index." If one makes use of the modes, the iron color index becomes further simplified. Thus, 50 mg of iron and 5,000,000 red blood cells become the standards or 100 per cent levels for men, while 45 mg of iron and 4,500,000 red blood cells represent 100 per cent levels for women. To illustrate. The iron color index of a man with an iron content of the blood of 40 mg per hundred cubic centimeters and an erythrocyte count of 4,800,000 would be  $\frac{\text{percentage of iron}}{\text{percentage of red blood cells}} = \frac{80}{96} = -1$ . Since in this equation both the iron content and the first two figures of the red blood cell count must be divided by 50 to determine the percentage of the normal of each, then

$$\frac{\text{percentage of iron}}{\text{percentage of red blood cells}} = \frac{\text{milligrams of iron in 100 cc of blood}}{\text{first two figures of red blood cell count}} = \frac{40}{48} = -1$$

For women both figures are divided by 45, and therefore the same formula obtains. Consequently, the iron color index based on our figures for the iron content of the blood of both sexes may be calculated simply by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the first two figures of the erythrocyte count

38 Murphy, W. P., Lynch, R., and Howard, I. M. Value of Determinations of Iron Content of Whole Blood, *Arch Int Med* 47:883 (June) 1931.

*Total Amount of Iron in the Blood Stream*—The figure 3 Gm of iron is often quoted as representing the total amount of iron present in the body. On the basis of 50 mg of iron per hundred cubic centimeters of blood and 85 cc of blood per kilogram of body weight, a man weighing 70 Kg, possessing approximately 6 liters of blood, has in the blood stream alone 3 Gm of iron. The total amount of iron in the body, if one includes the iron stored in the reservoirs, the liver and the spleen as well as the iron present in the nucleus of every cell in the body, is therefore more than this figure. A woman weighing 55 Kg, possessing 4.7 liters of blood, would have approximately 2 Gm of iron in the blood stream, taking 45 mg of iron per hundred cubic centimeters of blood as the standard.

#### EXPERIMENTAL DATA ON COPPER IN HUMAN BLOOD

*Normal Copper Content*—The series of one hundred and fifty determinations used to establish the average copper content of whole blood represents, so far as we know, the most substantial number reported in the literature.

The average copper content of the blood of the fifty normal men listed in table 1 was 0.141 mg or 141 micrograms per hundred cubic centimeters. The McFarlane<sup>31</sup> technic was employed in making this group of determinations. We have explained the difficulties encountered in the use of this method as well as our reasons for believing the results obtained to be somewhat high. We therefore employed the iron precipitation method for all the other determinations of copper reported.

The copper content of the blood of the fifty normal men listed in table 2 averaged  $0.132 \pm 0.0008$  mg per hundred cubic centimeters of blood. We have adopted this figure as the standard for normal men.

The figures for the blood copper of the fifty normal women listed in table 3 averaged  $0.131 \pm 0.0012$  mg per hundred cubic centimeters. Unlike the variations in the blood iron, the figures for the blood copper of the two sexes approximated each other. With regard to normal women we have already referred to the tendency toward the anemic state, a fact which explains the fluctuation in the iron content of their blood. Our studies on anemia, which we report later, lead us to think that there exists a reciprocal relationship between the iron and the copper content of the blood. As a rule, when we found a low iron content we found a high copper content. We are therefore inclined to the belief that the greater potentiality of anemia to develop in women probably calls out of reserve a greater quantity of hemopoietic stimulant in the form of copper. This mechanism may account for the presence in the blood of women of a larger quantity of copper in proportion to iron than is found in the blood of men. This also aids in interpreting the frequent finding of a high copper level coupled with a normal iron level in routine determinations on female patients.

*Total Copper in the Blood Stream*—The average man weighing 70 Kg has approximately 7.8 mg of copper in the blood stream. The figure for a woman weighing 55 Kg is approximately 6 mg of copper. The ratio of the total iron to the total copper of the blood is  $\frac{3,000}{7.8}$ , or 385:1, for the man and  $\frac{2,000}{6}$ , or 333:1, for the woman. These figures demonstrate that the blood copper of the average woman is greater in proportion to the blood iron than is the blood copper of the average man.

#### SUMMARY

*Copper*—The copper content of the whole blood of normal men has been determined by two methods. By one method we obtained an average for fifty normal men of 0.141 mg, or 141 micrograms, of copper per hundred cubic centimeters of blood. By a second method we obtained an average for another series of fifty normal men of  $0.132 \pm 0.0008$  mg.

We have adopted the latter figure as the normal because we have reason to believe that the method employed in the second series of determinations can be better controlled. The figures reported for the blood copper of normal women are also based on the latter method.

The average copper content of the whole blood of fifty normal women was  $0.131 \pm 0.0012$  mg per hundred cubic centimeters.

Although there is a marked difference between the iron content of the whole blood of normal men and that of normal women, no such difference existed for the blood copper. The blood copper is greater in proportion to the blood iron in women than in men. This is in harmony with the observation that women are more susceptible to anemia than are men. This greater susceptibility calls forth a relatively greater amount of copper to stimulate hematopoiesis.

*Iron*—The average iron content of the whole blood for two hundred normal men was  $50.13 \pm 0.15$  mg per hundred cubic centimeters, and for one hundred normal women,  $43.42 \pm 0.19$  mg.

The mathematical index, the mode, the figure which appears most frequently in the series of determinations and around which the majority of the figures group themselves, was 50 mg of iron per hundred cubic centimeters for the two hundred normal men and 45 mg for the one hundred normal women.

The fact that in women the average fell below the mode illustrates the tendency toward the anemic state in normal women.

We wish to emphasize further the accuracy with which the hemoglobin content may be estimated from the figures for the iron content and the facility with which hemoglobinometers may be standardized by the use of the method of determining the iron content.

On the basis of the fact that hemoglobin contains 0.335 per cent of iron, the average whole blood of normal men contains  $14.96 \pm 0.045$  Gm of hemoglobin per hundred cubic centimeters, while the average whole blood of normal women contains  $12.96 \pm 0.06$  Gm

Instead of the single standard for hemoglobin now employed clinically for both men and women, it would be more accurate to use one standard for men and another for women

Since the normal iron content for men is 50 mg per hundred cubic centimeters, one may state that this figure represents 100 per cent of hemoglobin. One can therefore convert with ease the iron content of the blood into the percentage of hemoglobin by multiplying the figure for the iron content per hundred cubic centimeters by 2. In the case of women, however, this conversion entails the multiplication of the figure for iron by 2.22, since the normal iron content of the blood of the average woman is 45 mg per hundred cubic centimeters

The iron color index, which may be substituted with greater accuracy for the old color index, may be obtained by dividing the number of milligrams of iron per hundred cubic centimeters of blood by the first two figures of the red blood cell count. This derivation of the index is based on our figures for the normal iron content of the whole blood of both sexes

## II BLOOD COPPER AND IRON IN MEN AND WOMEN WITH VARIOUS PATHOLOGIC CONDITIONS

Having determined the copper and the iron content of the whole blood of adult normal men and women, and using these figures as standards for comparison, we examined the blood of patients suffering from various diseases

The copper and the iron content of the whole blood, the red cell count, the percentage of hemoglobin, the iron index and the iron color index of thirty-two patients suffering from various diseases which tend to produce abnormal blood pictures are listed in table 5. Among the group were patients with pernicious anemia (treated and untreated), Banti's disease, acute myelogenous leukemia, chronic lymphatic leukemia, malaria, gastric hemorrhage, arsenic poisoning, nephritis and carcinoma

This study was undertaken to ascertain whether anemia due to a deficiency of copper occurs in man. The figures in table 5 show definitely that pathologic conditions associated with anemia are characterized by a high copper content of the blood. We have adopted the term "hypercupremia," to indicate such an increased copper level. In all our determinations thus far, we have not encountered hypocupremia in any pathologic condition

Generally speaking, we have observed an inverse relationship between the blood copper and the blood iron with a possible exception in nephritis. When the iron content was low, the copper con-

tent was high. The lower the figure we obtained for the blood iron, the higher the figure we could expect for the blood copper. Such a relationship is illustrated by the following findings: in patient 16 (with sickle cell anemia), blood iron, 24.51 mg, blood copper, 0.235 mg, in patient 17 (with Banti's disease), blood iron, 27.25 mg, blood copper, 0.187 mg, in patient 19 (with acute myelogenous leukemia), blood iron, 32.90 mg, blood copper, 0.24 mg, in patient 12 (with secondary anemia), blood iron, 39.05 mg, blood copper, 0.172 mg, and

TABLE 5—*Values for Copper and Iron in the Blood of Patients with Various Pathologic Conditions*

Name	Sex	Diagnosis	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemo- globin, Gm per 100 Cc	Iron Index	Iron Color Index
1 Bow	F	Pernicious anemia (treated)	4,200,000	0.170	41.30	12.33	9.83	0.98
2 Foy	M	Pernicious anemia (treated)	4,015,000	0.139	42.65	12.73	10.62	1.06
3 Sis	F	Pernicious anemia (treated)	2,490,000	0.136	41.30	12.33	16.59	1.66
4 Sla	M	Pernicious anemia (treated)	1,990,000	0.180	35.45	10.58	17.81	1.78
5 Hei	M	Pernicious anemia (untreated)	1,810,000	0.164	20.00	5.97	11.05	1.11
6 Boc	F	Pernicious anemia (untreated)	1,350,000	0.201	16.40	4.90	12.15	1.21
7 Pot	F	Pernicious anemia (untreated)	2,850,000	0.198	38.15	11.39	13.39	1.34
8 Gar	M	Secondary anemia	3,300,000	0.173	29.65	8.85	8.98	0.90
9 Cal	M	Secondary anemia	3,968,000	0.222	42.00	12.54	10.59	1.06
10 Wes	F	Secondary anemia	3,968,000	0.180	31.65	9.45	7.98	0.80
11 Gow	F	Secondary anemia	3,200,000	0.198	28.55	8.52	8.91	0.89
12 All	M	Secondary anemia	3,750,000	0.172	39.05	11.66	10.41	1.04
13 Cre *	M	Secondary anemia	4,224,000	0.167	35.45	10.58	8.39	0.84
14 Cre *	M	Secondary anemia	4,416,000	0.155	41.15	12.28	9.32	0.93
15 Wic	F	Secondary anemia	3,904,000	0.174	31.55	9.42	8.08	0.81
16 Bas	M	Sickle cell anemia	2,520,000	0.235	24.51	7.32	9.74	0.97
17 Cam	F	Banti's anemia	3,850,000	0.187	27.25	8.13	7.08	0.71
18 Mic	F	von Jaksch's anemia	3,230,000	0.211	35.20	10.51	10.90	1.09
19 Mik	M	Acute myelogenous leukemia	3,250,000	0.240	32.90	9.82	10.12	1.01
20 Mah	M	Chronic lymphatic leukemia	4,672,000	0.160	52.65	15.72	11.27	1.13
21 Lis	F	Chronic lymphatic leukemia	3,770,000	0.187	40.30	12.03	10.69	1.07
22 Mal	M	Malaria	3,475,000	0.158	39.05	11.66	11.24	1.12
23 Kul	M	Purpura	3,230,000	0.195	36.35	10.85	11.25	1.13
24 Joh	M	Arsenic poisoning	1,715,000	0.254	21.20	6.33	12.36	1.24
25 McG *	M	Nephritis	2,665,000	0.180	30.95	9.24	11.61	1.16
			1,880,000	0.145	22.05	6.58	11.73	1.17
26 And	M	Gastric hemorrhage	4,162,000	0.162	42.35	12.64	10.18	1.02
27 Die	F	Neurasthenia	4,288,000	0.162	39.85	11.90	9.29	0.93
28 Mor	F	Carcinoma of the ovary	3,968,000	0.150	44.45	13.27	11.20	1.12
29 Fri	F	Carcinoma of the ovary	4,252,000	0.176	38.45	11.48	9.04	0.90
30 St J	M	Carcinoma of the rectum	2,945,000	0.200	20.20	6.03	6.86	0.69
31 Law	M	Carcinoma of the rectum	4,544,000	0.172	38.75	11.57	8.53	0.85
32 Joy	F	Carcinoma of the breast	3,968,000	0.274	32.80	9.79	8.27	0.83
33 Wea	F	Carcinoma of the uterus	3,710,000	0.168	31.95	9.54	8.61	0.86

\* Two determinations were made on this patient

in patient 21 (with chronic lymphatic leukemia), blood iron, 40.3 mg, blood copper, 0.187 mg. Patient 20, with chronic lymphatic leukemia, showed hypercupremia despite a normal value of blood iron.

Patient 25, with chronic nephritis, showed the typical relationship of iron to copper which characterizes the anemic state with an iron content of 30.95 mg and a copper content of 0.18 mg. At a later date, despite the development of more severe anemia, represented by a blood iron content of 22.05 mg, the blood copper did not show the anticipated increase, but actually fell to 0.145 mg. In another patient with chronic nephritis (Miss S, for whom figures are not included in table 5), an iron content of 33.9 mg was accompanied by a copper content of 0.123 mg.

We are continuing the studies on the copper metabolism in chronic nephritis in an attempt to find an explanation for the discrepancies in the values for persons with this condition

With reference to our findings, we note that Warburg and Krebs<sup>39</sup> mentioned an increase in the copper content of the serum of pigeons that were bled Sheldon and Ramage,<sup>40</sup> examining twenty-eight specimens of human blood spectroscopically, observed the strongest copper lines in the blood of a patient with anemia following hemorrhage and in that of a patient with carcinoma In seven cases of anemia in children, Gorter, Grendel and Weyers<sup>41</sup> found an elevated copper level in the whole blood The serum copper level was also high in several cases of anemia reported by Locke, Main and Robash<sup>42</sup> None of these investigators, however, determined the copper content of the whole blood with relation to the iron content of the whole blood

The work of Gorter, Grendel and Weyers deserves special comment, for they are the only investigators who reported copper determinations on the whole blood in anemia Their determinations were made by the use of the electrolytic method for the separation of copper Sarata<sup>24</sup> and Elvehjem and Lindow<sup>28</sup> discarded this method because of the failure to obtain accurate results when small samples of blood were used Flinn and Inouye<sup>7</sup> electrolyzed the material for twenty-four hours in order to plate out all of the copper from blood ash Using a micro-electrolytic apparatus, we were unable to plate out more than 70 per cent of the copper in twelve hours Gorter and his associates, however, claimed 100 per cent accuracy with the electrolytic method run for twenty minutes

#### COPPER AND IRON IN THE BLOOD OF A PATIENT WITH POLYCYTHAEMIA VERA

Our blood findings for a patient with polycythaemia vera serve to verify the inverse relationship between copper and iron Before treatment with phenylhydrazine was instituted, this patient, a woman, 60 years of age, had a normal value for copper in the blood despite an abnormally elevated erythrocyte count and a high value for iron After a few weeks of treatment with phenylhydrazine, marked changes in the

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39 Warburg, O., and Krebs, H. A. Ueber locker gebundenes Kupfer und Eisen im Blutserum, *Biochem Ztschr* **190** 143, 1927

40 Sheldon, S. H., and Ramage, H. Spectrographic Analysis of Human Tissues, *Biochem J* **25** 1608, 1931

41 Gorter, E., Grendel, F., and Weyers, W. A. M. Le rôle du cuivre dans l'anémie infantile, *Rev franc de pédiat* **7** 747, 1931

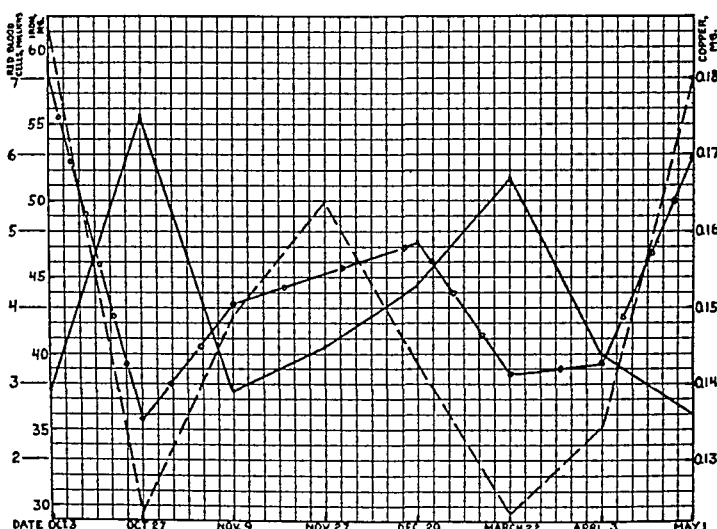
42 Locke, A., Main, E. R., and Robash, D. O. Copper and Non-Hemoglobinous Iron Contents of Blood Serum in Disease, *J Clin Investigation* **11** 527 (May) 1932



blood picture were observed. While the erythrocyte count and iron content fell sharply, the copper content of the blood rose. The drug was then omitted, and liver and iron were administered. As a result, the red blood cell count and the iron content of the blood rose, while the copper content fell.

TABLE 6—*Red Blood Cell Count and Copper and Iron Content of the Whole Blood in a Patient with Polycythæmia Vera*

Date	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Comment
10/ 3/33	7,040,000	0.139	60.95	Treatment with phenylhydrazine begun
10/27/33	2,592,000	0.175	29.40	Treatment stopped
11/ 9/33	4,063,000	0.139	42.50	
11/29/33	4,416,000	0.145	50.00	Treatment resumed
12/20/33	4,896,000	0.153	39.37	
3/28/34	3,072,000	0.167	29.55	Treatment stopped
4/ 3/34	3,296,000	0.144	35.20	
5/ 1/34	5,952,000	0.136	57.80	



A graph showing the fluctuation in values for iron and copper in the blood of a patient with polycythæmia vera. The broken line with the open circles represents the red blood cell count in millions per cubic millimeter of blood, the solid line represents the values for copper in milligrams per hundred cubic centimeters of blood, and the broken line represents the values for iron in milligrams per hundred cubic centimeters of blood.

The fluctuations in the red cell count and in the iron and the copper content of the blood in periods of treatment with phenylhydrazine and in periods in which treatment was not given are illustrated in the chart.

#### COPPER AND IRON IN THE BLOOD OF PATIENTS WITH TUBERCULOSIS

We have determined the copper and the iron content of the blood of ten men and ten women suffering from tuberculosis. The findings are listed in tables 7 and 8.

The tuberculous patients were in a sanatorium and had been under treatment for some time when samples of blood were drawn for analysis. Patient 1 in the series of men had a normal iron and copper content of the blood. His was classed as an arrested case, and he was about to be discharged. Patients 5 and 9 in the group of women and patients 2, 4, 5 and 6 in the group of men had a normal iron content, but the copper content was high. All the other patients showed a low

TABLE 7—*Values for Copper and Iron in the Blood of Ten Men with Tuberculosis*

Name	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
1. Now	4,550,000	0.129	52.15	15.57	11.46	1.15
2. Fra	5,000,000	0.154	51.30	15.31	10.26	1.03
3. Jen	4,700,000	0.163	47.35	14.13	10.07	1.01
4. Wel	4,510,000	0.179	51.10	15.25	11.33	1.10
5. Swa	5,000,000	0.169	49.50	14.78	9.90	0.99
6. O'Sh	4,530,000	0.171	49.00	14.63	10.82	1.08
7. Wad	4,280,000	0.207	43.45	12.97	10.15	1.02
8. Kom	4,680,000	0.208	44.25	13.21	9.46	0.90
9. Ang	3,950,000	0.207	42.00	12.54	10.63	1.06
10. Cla	4,200,000	0.234	38.30	11.43	9.12	0.91
Average	4,540,000	0.182	46.84	13.98	10.32	1.03

TABLE 8—*Values for Copper and Iron Determined on the Blood of Ten Women with Tuberculosis*

Name	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
1. Wig	4,030,000	0.225	38.15	11.39	9.46	0.95
2. Min	3,700,000	0.222	38.75	11.57	10.47	1.05
3. Hic	4,420,000	0.247	40.65	12.13	9.20	0.92
4. For	4,210,000	0.186	41.30	12.33	9.81	0.98
5. Mic	4,480,000	0.163	46.10	13.76	10.29	1.03
6. Con	4,250,000	0.216	40.45	12.08	9.52	0.95
7. Wil	4,025,000	0.183	38.48	11.49	9.56	0.96
8. Swa	4,050,000	0.174	42.35	12.64	10.46	1.05
9. Hun	4,200,000	0.154	48.55	14.49	11.56	1.16
10. McC	3,700,000	0.183	39.20	11.70	10.59	1.06
Average	4,107,000	0.195	41.40	12.36	10.09	1.01

iron level and a high copper level. The hypercupremia in the series of tuberculous patients was characteristic of disease syndromes in which chronic sepsis and fever are present. It may have been the result of the failure on the part of the liver or bone marrow to store or utilize the metal. The anemia of tuberculosis may be the result of hemorrhage, but it is usually myelophthysic, that is, it arises from a depression of the bone marrow. If the bone marrow is depressed, the utilization of copper may also be inhibited, thus accounting for the increased amounts remaining in the circulation.

The hypercupremia in tuberculous patients may, on the other hand, be a mobilization of copper for purposes of catalysis. What associations the increased copper level has with respiration and with

various processes of oxidation and reduction is problematic. The relationship to hematopoiesis is more apparent. From an examination of the figures, especially those for the male patients, the copper level seems to be definitely linked with the severity of the anemia or with the iron level. The hypercupremia of tuberculosis may therefore coincide with the inverse relationship of copper to iron, which is characteristic of anemia.

#### COMMENT

In milk anemia of rats, copper in the presence of iron is effective, when used in small doses, in increasing the hemoglobin concentration and the red blood cell count. Since copper is not part of the hemoglobin molecule, Elvehjem, Steenbock and Hart<sup>23</sup> maintained that this metal functions as a catalyst. Its presence makes possible the utilization of the building stones, iron and protein, necessary for the manufacture of hemoglobin and erythrocytes. Since all the other factors necessary for hematopoiesis are present, the result is especially dramatic when the deficiency is corrected by the addition of copper. Equally striking is the reaction in the anemia of pellagra, which is amenable only to treatment with vitamin B<sub>2</sub>, of scurvy, which responds only to the administration of vitamin C, and of hypothyroidism, which is corrected only by the administration of thyroid. If, on the other hand, a building stone is missing, as in the deficiency of protein in famine anemia and in the deficiency of iron in primary hypochromic anemia, the response is slower and is dependent on the quantity and frequency of intake of the missing factor.

Is copper a specific requirement for man? One cannot always apply the results of experimentation on animals to man. Even the work of Whipple and Robscheit-Robbins<sup>43</sup> on the hemorrhagic anemia of dogs, which anticipated the discovery of the specificity of liver for pernicious anemia, is as yet not directly applicable to man. Pernicious anemia is not a disease of dogs. The stomach and liver of the dog contain very little of the substances effective in the treatment of pernicious anemia in man.<sup>44</sup>

Copper falls into the category of hematopoietic catalysts, which includes thyroxine, vitamins B<sub>2</sub> and C and sunshine and possibly other factors which have not been discovered. Beard, Johnson and Andes<sup>45</sup>

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43 Whipple, G. H., and Robscheit-Robbins, F. S. Simple Experimental Anemia and Liver Extracts, *Proc Soc Exper Biol & Med* **24** 860 (June) 1927.

44 Richter, O., Ivy, A. C., and Meyer, A. F. A Study of the Dog's Stomach and Liver for Substances Effective in Pernicious Anemia, *Proc Soc Exper Biol & Med* **31** 550 (Feb.) 1934.

45 Beard, H. H., Johnson, A. G., and Andes, E. J. Effect of Radiant Energy With and Without Iron upon Nutritional Anemia in the Rat, *Proc Soc Exper Biol & Med* **31** 23 (Oct.) 1933.

corrected the anemia of rats on copper-free milk diets by the use of sunshine and iron. This opens a new avenue of thought with respect to these catalysts. It may be possible that the effect produced by any one may be replaced by another.

The habitat of the rat family is essentially devoid of sunlight. The importance of copper in the rat's hematopoietic system may be an adaptation, just as the ability of this animal to manufacture vitamin C is a characteristic born of necessity. Early experimentation immediately stamped the rat unfit for studies on vitamin C. In this animal, belonging to a scavenger family which infrequently feeds on fresh foods, there has developed this faculty of intrinsic preparation of this essential with which other animals and man must be supplied ready for use in the form of antiscorbutic foods. An analogous situation may exist with regard to the importance of copper in the rat as compared with the need for it in man. The figures of Warburg and Krebs<sup>39</sup> on the copper content of the serum of various animals show that the rat possesses the highest copper level. This further emphasizes the possible need in the case of the rat for a high copper content of the blood to substitute for other hematopoietic catalysts.

The conditions of the experiments on animals in which copper was shown to be a requirement are also highly artificial and give promise of little practical application to studies on human beings. Even the iron salts in the diet were specially purified to avoid contamination by copper. Parsons<sup>46</sup> stated that clinically when iron fails to correct anemia the addition of copper is of no avail because of the usual presence of recognizable quantities of copper in iron salts. We know from our experience with reagents and even with distilled water that traces of copper are always present. We have found copper in ordinary drinking water. A diet which includes vegetables, fruits, liver and other internal organs, sea foods and pasteurized milk is comparatively rich in copper. Although this fact does not rule out any important rôle that copper may play when it is ingested, it at least indicates that a copper-free or even a copper-poor diet is possible only in a person on a very restricted intake.

Even though the copper intake is low, a sufficient supply is maintained through the quantities of the metal stored in the liver and in other organs. This is true for a human being more than for a rat in the experimental cage. Recognizing this fact, Schultze and Elvehjem<sup>47</sup> recently accounted for the failure of copper to assume greater importance in the clinical treatment of anemia by citing the large quantities

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46 Parsons, L. G. Anemias of Infancy and Early Childhood, Some Observations, *J. A. M. A.* **97** 973 (Oct 3) 1931.

47 Schultze, M. O., and Elvehjem, C. A. The Relation of Iron and Copper to the Reticulocyte Response in Anemic Rats, *J. Biol. Chem.* **102** 357 (Oct) 1933.

stored by man. This was evident in our studies of the blood copper in cases of blood dyscrasia in which, despite the existence of long-standing anemia, hypercupremia was maintained.

The most likely conclusion to be drawn from the finding of a high copper content in almost all cases of anemia is that the copper is brought into use from the body reservoirs to stimulate hematopoiesis. Other possibilities suggest themselves which demand consideration and study. Anemia caused by a deficiency of copper may exist in an infant given an unsupplemented milk diet throughout the first year of life. In an adult on a highly restricted milk diet, such as the milk diet for gastric or duodenal ulcer maintained for a long period of time, such a condition may likewise ensue. Furthermore, just as hyperglycemia in diabetes does not denote an increased utilization of carbohydrate, so hypercupremia may not necessarily indicate an increased utilization of copper. Failure of the bone marrow or liver to employ the copper or a reduced elimination of copper from the body may be responsible for the higher copper level. Anemia may be associated with, or in some cases may be the result of, a disturbance in the copper metabolism.

It seems that hypercupremia represents a response to an emergency and that the mobilization of copper is effected to combat the anemia. We recognize the significant part that copper plays in hematopoiesis, but we postulate that in man, at least, sufficient copper is stored and made available during emergencies to minimize the possible occurrence of anemia caused by a deficiency of copper. We are continuing with a study of this problem.

#### SUMMARY

We have designated an increase in the copper content of the blood as hypercupremia and a decrease in the copper content of the blood as hypocupremia. An increased copper concentration, or hypercupremia, was observed in various conditions with abnormal blood pictures, such as secondary anemia, pernicious anemia, von Jaksch's anemia, sickle cell anemia, Banti's disease, malaria, myelogenous leukemia, arsenic poisoning and carcinoma.

An inverse relationship exists between the copper and the iron content of the blood in anemia. As the iron content falls the copper content tends to rise. Hypercupremia is the usual response to hypoferronemia.

The inverse relationship of copper and iron in anemia is clearly illustrated in a case of polycythaemia vera. When first examined the patient's blood iron content was extraordinarily high, while the copper content was normal. Treatment with phenylhydrazine resulted in temporary anemia. The low iron content was associated with hypercupremia. When the administration of phenylhydrazine was discon-

tinued, and liver and iron therapy was instituted, the iron content rose and the copper content fell

Tuberculosis is also characterized by hypercupremia. The average copper content of the blood of ten men with tuberculosis was 0.182 mg per hundred cubic centimeters, and that of ten women with tuberculosis was 0.195 mg.

The hypercupremia of tuberculosis most likely coincides with the inverse relationship of copper and iron in the blood which obtains in anemia. The anemia which is often found in tuberculosis is probably the factor most responsible for the increased copper level of the blood.

That copper plays a significant rôle in hematopoiesis is suggested by its increase in the blood stream in almost all anemic states. Our figures indicate that the majority of patients with anemia, regardless of its chronicity or severity, show hypercupremia. It is evident, therefore, that sufficient quantities are stored for and made available in emergencies. This fact minimizes the possibility of the occurrence of anemia caused by the deficiency of copper in man.

### III BLOOD COPPER AND IRON IN PREGNANCY AND IN THE NEW-BORN

We made determinations of the copper and the iron content of the blood of twenty-five pregnant women in various months of gestation. The findings are presented in table 9. The blood copper of the average parturient, which was 0.195 mg per hundred cubic centimeters, represents a 50 per cent increase over the figure (0.131 mg) which we reported as the average copper content for fifty normal women who were not pregnant. Taking into consideration the increase in the blood volume in pregnancy, which at term reaches the extent of 23 per cent in the average case,<sup>48</sup> the total amount of copper in the blood stream in pregnancy is actually about twice the amount present in the non-gravid state. Instead of the 6 mg of copper present in the entire volume of blood of the average woman, as much as 12 mg may be found in the blood of the pregnant woman.

The average iron content of the blood for the series of pregnant women, which was 40.44 mg per hundred cubic centimeters, was below the figure (45 mg) which we reported as the mode for 100 normal women, and therefore represents anemia, while the average copper content (0.195 mg) was above the average for normal women and represents hypercupremia. On examining individual subjects, however, we found two significant types of blood picture in pregnancy. In one type, a normal iron content, or one slightly below normal, was accom-

48 Dieckman, W. J., and Wegner, C. R. The Blood in Normal Pregnancy. I. Blood and Plasma Volumes, *Arch. Int. Med.* **53**: 71 (Jan) 1934.

panied by a high copper content. Patients 1, 4, 7, 8, 13, 18, 20 and 25 presented such a picture. The high copper level despite the normal iron level may be explained by the fact that the maternal blood transports copper to the fetus. The fetal liver has been found to contain from six to ten times as much copper per kilogram of weight as does the adult human liver. Sheldon<sup>49</sup> stated that 7 mg of copper is stored in the liver of a new-born infant.

In the second type of blood picture we found true anemia. In this type a low iron content was associated with a high copper content. To

TABLE 9—*Values for Copper and Iron in the Blood of Twenty-Five Pregnant Women*

Name	Month	Red Blood Cells	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc	Hemoglobin, Gm per 100 Cc	Iron Index	Iron Color Index
1 Smi	6	4,400,000	0.147	43.35	12.94	9.85	0.99
2 Han	5	3,500,000	0.186	34.85	10.40	9.96	1.00
3 Bai	7	3,750,000	0.212	29.95	8.94	7.99	0.80
4 Kom	5	4,550,000	0.221	43.65	13.03	9.59	0.96
5 Sta	7	4,450,000	0.256	38.90	11.61	8.74	0.87
6 Ful	5	4,000,000	0.178	42.35	12.64	10.57	1.06
7 Gre	5	3,900,000	0.215	43.45	12.97	11.14	1.11
8 Wei	6	4,200,000	0.212	44.25	13.21	10.54	1.05
9 Suc	9	4,500,000	0.197	41.30	12.33	9.18	0.92
10 McI	5	3,500,000	0.188	36.20	10.81	10.34	1.03
11 Mai	9	4,400,000	0.175	42.20	12.60	9.59	0.96
12 Wat	9	4,150,000	0.269	38.45	11.48	9.27	0.93
13 Obe	9	4,400,000	0.147	45.45	13.57	10.33	1.03
14 Sme	5	4,150,000	0.195	39.20	11.70	9.45	0.95
15 Boy	5	4,350,000	0.203	43.45	12.97	9.99	1.00
16 Hol	9	3,850,000	0.172	37.30	11.13	11.13	1.11
17 Unt	6	3,700,000	0.216	36.50	10.90	9.87	0.99
18 Var	5	4,200,000	0.167	43.10	12.87	10.26	1.03
19 Jac	7	3,950,000	0.250	39.85	11.90	10.09	1.01
20 Thi	9	3,950,000	0.200	42.90	12.81	10.86	1.09
21 Wil	5	3,950,000	0.180	42.90	12.81	10.86	1.09
22 McA	8	4,000,000	0.138	41.00	12.24	10.25	1.03
23 Cen	5	3,300,000	0.153	37.05	11.06	11.23	1.12
24 Bag	5	4,000,000	0.212	40.00	11.94	10.00	1.00
25 Chr	8	3,800,000	0.177	43.45	12.97	11.43	1.14
Average		4,016,000	0.193	40.44	12.07	10.10	1.01

cite an example, patient 3 had a red cell count of 3,500,000, an iron content of 29.95 mg and a copper content of 0.212 mg per hundred cubic centimeters. The figures for patients 2, 5, 10, 12, 14, 16, 17 and 23 illustrate this type. The hypercupremia of pregnancy may therefore be more than the result of the transfer of comparatively large quantities of copper from the maternal blood to the fetus. In the event of anemia complicating pregnancy it may also represent an effort on the part of the mother to mobilize a hematopoietic stimulant. Such a mobilization of copper coincides with the hypercupremia which we found in anemias other than that of pregnancy. The pregnant women in our series were patients who presented themselves at the clinic for antepartum care. Despite the fact that the determinations on the blood were

49 Sheldon, J. H. Some Considerations on the Influence of Copper and Manganese on the Therapeutic Activity of Iron, *Brit. M. J.* 2: 869 (Nov. 12) 1932.

made during the hot months of July and August, when dehydration reduces the plasma volume and the iron content of the blood tends to increase, the average blood iron content of these women was below par. This so-called physiologic anemia of pregnancy occurs in a high percentage of patients in the clinic.

Other investigators also have determined the blood copper in pregnancy. Their results are based either on too small a group or on determinations on the blood serum instead of on whole blood. Krebs<sup>50</sup> reported a series of determinations of copper on the blood serum of nineteen pregnant women. His average finding for the group indicated that the serum copper was twice as high during pregnancy as in the nongravid state. Gorter, Grendel and Weyers<sup>41</sup> reported an increased copper level in the blood of seven pregnant women. Sheldon and Ramage,<sup>40</sup> using a spectroscopic method, observed a strong copper line in a case of severe anemia of pregnancy. Locke, Main and Robash<sup>42</sup> reported a high copper level in the serum of four pregnant women.

#### COMPARISON OF FETAL AND MATERNAL BLOOD

We have examined and compared the blood of the new-born, taken from the umbilical cord, with the maternal blood drawn immediately before delivery. The following interesting results were obtained:

Specimens of Blood	Copper, Mg per 100 Cc	Iron, Mg per 100 Cc
1 Maternal	0.183	42.00
Fetal (male)	0.076	53.45
2 Maternal	0.230	39.85
Fetal (male)	0.071	43.65
3 Maternal	0.293	43.10
Fetal (female)	0.075	50.20
4 Maternal	0.194	38.30
Fetal (female)	0.098	50.00
5 Maternal	0.189	34.50
Fetal (male)	0.089	54.65

In this series the average copper content of the maternal blood, which was 0.219 mg per hundred cubic centimeters, is characteristic of the hypercupremia of pregnancy. The average copper content of the new-born, which was 0.082 mg per hundred cubic centimeters, represents a comparatively low level. In case 3 the maternal blood was four times as rich in copper as was the fetal blood. Moreover, the figures for cases 1, 2 and 3 indicate that the new-born infants possessed, per unit volume of blood, only a little more than half of the copper found in the average normal adult.

On receiving the copper which is diffused through the placenta, the fetus does not retain the bulk of the element in the blood stream but evidently stores it in the liver. The fact that the liver and the spleen

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50 Krebs, H. A. Ueber das Kupfer im menschlichen Blutserum, *Klin Wchnschr* 7: 584, 1928.



serve as the reservoirs for the greater portion of the copper in the fetus may be associated with the importance of these organs as hematopoietic centers in the embryo. In the normal adult the manufacture of erythrocytes is exclusively the function of the bone marrow. It is true that copper performs its biologic function chiefly in the bone marrow by stimulating the formation of hemoglobin and the maturation of erythrocytes, the blood of the adult should be relatively rich in this element. The sinusoids of the bone marrow in which the red cells are manufactured are part of the closed circulatory system, and a high level of copper in the blood would therefore be necessary to maintain a sufficient supply for these erythropoietic centers. These facts serve to explain the differences between the blood copper of the fetus and that of the normal adult.

The polycythemia of the new-born accounts for the high iron content of the blood drawn from the umbilical cord. The average iron content of the fetal blood in the five cases was 50.39 mg, compared with 39.55 mg in the maternal blood. The relatively high level of iron in the blood is maintained in the fetus, as in case 5 (54.65 mg), even when the maternal blood (34.5 mg) shows definite anemia.

#### SUMMARY

We have made determinations of the copper content of the whole blood of twenty-five pregnant women. The average for the series, which was 0.195 mg per hundred cubic centimeters, represents a 50 per cent increase over the average (0.131 mg) for fifty normal women who were not pregnant. Hypercupremia seems to be a constant finding in pregnancy.

If one takes into consideration the increase in blood volume in pregnancy, which in the average case occurs to the extent of 23 per cent, the total amount of copper present in the blood stream of the parturient woman is twice the amount present in the blood stream of the normal woman who is not pregnant.

Determinations were made of the iron content of the whole blood of the twenty-five pregnant women. The average value, which was 40.44 mg per hundred cubic centimeters, is below the figure (45 mg) which we have established as the mode for one hundred normal women who were not pregnant. Relative anemia usually accompanies pregnancy.

Hypercupremia of pregnancy, when associated with a normal iron content, is physiologic and reflects the normal mechanism of transporting copper from the maternal blood to the fetal reservoirs. Hypercupremia of pregnancy, when accompanied by hypoferronemia, may represent not only this mechanism but also mobilization of copper to combat the anemia which is commonly found in the pregnant state.

A comparison of the blood of the new-born and that of the mother was made in five cases. The maternal blood was from two to four times as rich in copper as was the blood of the umbilical cord, whereas the iron content of the blood of the new-born infant was always at a higher level than was the iron content of the blood of the mother.

A relatively high iron content may be maintained in the blood of the fetus even when the maternal blood shows definite hypoferronemia.

The copper content of the blood of the umbilical cord, which averaged 0.082 mg per hundred cubic centimeters, was only a little more than one-half as high as that of the average normal adult.

In the normal adult hematopoiesis is the exclusive function of the bone marrow, and the blood copper is maintained at a relatively high level to supply the sinusoids, which are in direct communication with the blood stream, with the hematopoietic stimulant. In the fetus, since the liver and the spleen are centers for hematopoiesis, there is probably a mobilization of copper in these organs instead of in the blood.

# REACTION ( $p_H$ ) AND CARBON DIOXIDE CONTENT OF THE VENOUS PLASMA IN PERNICIOUS ANEMIA

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AND

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That there is a distinct interrelationship between the gastric secretory mechanism and the acid-base balance of the blood has been definitely shown in the literature (Hermanns and Sakr,<sup>1</sup> Bakaltschuk,<sup>2</sup> Apperly and Crabtree,<sup>3</sup> Browne and Vineberg<sup>4</sup> and others) Hermanns and Sakr, who studied patients in whom the secretion was abnormal, reported that gastric hyperacidity is characterized by a low alkali reserve of the blood and achylia by a high reserve

Studies of the acid-base balance that have been conducted on patients with pernicious anemia, in whom there is a complete dysfunction of the gastric glands, without exception have indicated abnormalities in the alkali reserve or in the reaction of the blood associated with this disease Kahn and Barsky<sup>5</sup> (1919), Gettler and Lindeman<sup>6</sup> (1920) and Ashby<sup>7</sup> (1925) reported a lowered alkali reserve in the majority of the cases studied, indicating acidosis, whereas, on the other hand, Barr and Peters<sup>8</sup> (1921), Dautrebande<sup>9</sup> (1925), Dill and his

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From the Lilly Laboratory for Clinical Research of the Indianapolis City Hospital

1 Hermanns, L, and Sakr, J M Ueber die Regulierung des Saurebasengleichgewichtes bei den Sekretionsstorungen des Magens, *Klin Wchnschr* **6** 1367 (July 16) 1927

2 Bakaltschuk, M Der Magen als Mitregulator des Saurebasengleichgewichts, *Klin Wchnschr* **7** 1551 (Aug 12) 1928

3 Apperly, F L, and Crabtree, M G The Relation of Gastric Function to the Chemical Composition of the Blood, *J Physiol* **73** 331 (Dec) 1931

4 Browne, J S L, and Vineberg, A M The Interdependence of Gastric Secretion and the CO<sub>2</sub> Content of the Blood, *J Physiol* **75** 345 (July) 1932

5 Kahn, M, and Barsky, J Studies of the Chemistry of Pernicious Anemia, *Arch Int Med* **23** 334 (March) 1919

6 Gettler, A O, and Lindeman, Edward Blood Chemistry of Pernicious Anemia, *Arch Int Med* **26** 453 (Oct) 1920

7 Ashby, W Blood Volume VI The Relationship Between Blood Volume, Total Corpuscle Content and Alkaline Reserve in Cases of Pernicious Anemia, *Arch Int Med* **36** 24 (July) 1925

8 Barr, D P, and Peters, J P, Jr III The Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of the Blood in Severe Anemia, *J Biol Chem* **45** 571 (Feb) 1921

9 Dautrebande, L L'alcalose paradoxale de l'anémie perniciouse, *Compt rend Soc de biol* **93** 1031 (Oct 30) 1925

co-workers<sup>10</sup> (1928) and Hitztenberger and Tuchfeld<sup>11</sup> (1931), largely on the basis of experimentally derived curves of the carbon dioxide absorption, postulated the existence of alkalosis in this disease

With the hope of throwing more light on this phase of pernicious anemia, twenty-nine patients with typical pernicious anemia have been studied relative to the hydrogen ion concentration and the carbon dioxide content of the venous blood, and the data have been compared with those obtained from a series of sixteen normal subjects

The patients with pernicious anemia were grouped according to the red blood cell counts and according to the degree of involvement of the central nervous system. Since alkalosis in itself is known to be capable of producing paresthesia in diseases other than pernicious anemia, an attempt has been made to correlate the possible relationship between the acid-base equilibrium in pernicious anemia and the clinical manifestations of involvement of the central nervous system

Weiss, Kiss and Kuszling,<sup>12</sup> in a paper relating to the reaction of the blood and to hemopoiesis, suggested that the clinical improvement following the administration of hydrochloric acid might be due in some degree to the lowering of the  $p_H$  of the blood. In order to note any appreciable changes in the acid-base equilibrium of the blood we determined the  $p_H$  and the carbon dioxide content of the venous blood in a series of patients with pernicious anemia before and after the daily administration by mouth of from 6 to 10 cc of a dilute solution (10 per cent) of hydrochloric acid

#### PROCEDURE AND METHODS

The blood was drawn in each case from a large vein of the arm, after stasis of less than one minute, into an oiled syringe and introduced under oil into a centrifuge tube coated with a sufficient amount of potassium oxalate to yield a concentration of 3 mg of oxalate per cubic centimeter of blood. Following replacement of the layer of oil by paraffin of a low melting point, the blood was immediately centrifugated, the separated plasma, sampled through a hole bored under oil through the paraffin, was promptly analyzed for the  $p_H$  and the carbon dioxide content. The  $p_H$  was determined according to Hastings and Sendroy's<sup>13</sup> bicolor

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10 Dill, D B, Bock, A V, van Caulaert, C, Folling, A, Hurxthal, L M, and Henderson, L J. Blood as a Physiochemical System. VII The Composition and Respiratory Exchanges of Human Blood During Recovery from Pernicious Anemia, *J Biol Chem* **78** 191 (June) 1928

11 Hitztenberger, K, and Tuchfeld, F. Die Blutreaktion der perniziösen Anämie im schlechten und guten Zustand, *Ztschr f klin Med* **117** 607, 1931

12 Weiss, S, Kiss, F, and Kuszling, N. Ueber den Einfluss der Wasserstoffionenkonzentration des Blutes auf die Zahl der roten Blutkörperchen, *Ztschr f d ges exper Med* **60** 58, 1928

13 Hastings, A B, and Sendroy, J, Jr. Studies of Acidosis. XX The Colorimetric Determination of Blood  $p_H$  at Body Temperature Without Buffer Standards, *J Biol Chem* **61** 695 (Oct) 1924

modification of Cullen's method, the manometric method of Van Slyke and Neill<sup>14</sup> was employed in the determination of the carbon dioxide content. From the  $p_{\text{H}}$  and the carbon dioxide content of the plasma, the carbon dioxide tension was calculated graphically by means of the line chart of Van Slyke and Sendroy<sup>15</sup>

All samples of blood were drawn between the hours of 9 and 11 a m. Experiments confirming the reports of Cullen and Earle<sup>16</sup> were performed, indicating that the effect of breakfast was a negligible factor, so that we felt justified in assuming that the values obtained in each case represented basal conditions. All analyses were performed during July and August.

## RESULTS

*Normal Subjects*—In table 1 are presented the results of the analyses of the venous plasma obtained from sixteen normal persons.

TABLE 1—*The  $p_{\text{H}}$ , Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Sixteen Normal Subjects*

Subject	Age, Years	Sex	$p_{\text{H}}$	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Tension, Mm
1	22	M	7.37	66.5	50.0
2	23	F	7.38	55.9	41.6
3	24	M	7.35	62.0	48.8
4	23	F	7.37	60.5	45.5
5	23	F	7.38	61.8	46.0
6	26	F	7.36	57.0	44.5
7	22	F	7.39	55.1	40.0
8	19	M	7.38	55.2	41.2
9	33	M	7.37	61.4	46.4
10	21	M	7.34	67.1	54.0
11	23	M	7.37	66.8	51.0
12	24	M	7.34	64.9	52.8
13	21	F	7.37	55.9	42.0
14	22	F	7.38	61.6	45.8
15	36	M	7.37	67.7	51.0
16	21	F	7.38	54.7	40.5
Mean value			7.37 $\pm$ 0.003*	61.5 $\pm$ 0.84*	46.4 $\pm$ 0.82*
Coefficient of variation			0.2	7.8	9.5

\* Probable error of the mean

The range of the  $p_{\text{H}}$  for the normal group was from 7.34 to 7.39. The average  $p_{\text{H}}$  was 7.37. Crimm and Watson<sup>17</sup> reported an average  $p_{\text{H}}$  of

14 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61**: 523 (Sept.) 1924.

15 Van Slyke, D. D., and Sendroy, J. Jr. Studies of Gas and Electrolyte Equilibria in Blood. XV. Line Charts for Graphic Calculations by the Henderson-Hasselbalch Equation, and for Calculating Plasma Carbon Dioxide Content from Whole Blood Content, *J. Biol. Chem.* **79**: 781 (Oct.) 1928.

16 Cullen, G. E., and Earle, I. P. Studies of the Acid-Base Condition of Blood. II. Physiological Changes in Acid-Base Condition Throughout the Day, *J. Biol. Chem.* **83**: 545 (Sept.) 1929.

17 Crimm, P. D., and Watson, H. L. Vitamin Therapy in Pulmonary Tuberculosis. IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Diet, *Ann. Int. Med.* **7**: 109 (July) 1933.

7.37 for fifty normal persons and Woodward and her co-workers,<sup>18</sup> an average value of 7.38 for twenty-five normal subjects

The carbon dioxide content ranged from 54.7 to 67.7 volumes per cent, the mean approximating 61.5 volumes per cent. Earle and Cullen<sup>19</sup> reported the normal range of the total carbon dioxide content of the venous plasma to lie between 55 and 74 volumes per cent.

The calculated carbon dioxide tension varied in this group of normal subjects from 40.5 to 54 mm., averaging approximately

TABLE 2—*The  $p_H$ , Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Twenty-Nine Patients with Pernicious Anemia*

Patient	Age, Years	Sex	Red Blood Cells, Millions per C. Mm.	Hemo globin, per Cent*	Involvement of Central Nervous System	$p_H$	Carbon Dioxide Content, Volumes per Cent	Carbon Dioxide Tension, Mm.
1	74	M	4.50	94.3	Advanced	7.34	57.8	46.5
2	39	F	1.67	32.7	None	7.47	58.8	36.0
3	55	M	2.90	63.7	Moderate	7.30	56.8	50.0
4	65	M	4.90	98.3	None	7.43	53.3	35.7
5	41	F	4.93	90.5	Early	7.38	57.0	42.3
6	46	M	5.28	85.0	Early	7.41	58.9	40.5
7	57	M	5.52	86.0	Advanced	7.38	55.6	41.5
8	66	M	5.05	83.0	Advanced	7.39	58.3	42.5
9	36	M	4.69	78.2	None	7.39	59.5	43.0
10	63	F	5.64	95.6	Early	7.37	60.8	46.0
11	57	M	3.33	60.2	Advanced	7.41	60.8	41.8
12	64	M	4.64	84.0	Advanced	7.39	60.0	43.3
13	55	F	5.30	78.2	Advanced	7.37	61.9	46.5
14	38	F	4.04	69.5	Early	7.39	54.4	39.8
15	57	M	4.15	67.4	Early	7.40	56.8	40.0
16	48	M	4.95	87.1	Advanced	7.38	59.9	44.2
17	59	F	5.03	70.2	Early	7.37	57.1	43.0
18	63	M	5.67	109.4	Moderate	7.36	61.8	47.8
19	54	M	2.85	47.1	Moderate	7.37	57.2	43.0
20	63	F	3.76	34.6	Moderate	7.37	53.3	40.0
21	58	M	4.09	78.2	Advanced	7.36	57.6	42.8
22	47	F	3.98	70.2	Advanced	7.36	49.4	38.2
23	43	M	4.50	68.8	Early	7.39	59.1	42.8
24	51	F	4.58	68.8	Moderate	7.38	63.4	47.0
25	55	M	4.79	94.3	Advanced	7.37	63.3	47.8
26	65	F	2.00	53.5	Moderate	7.39	63.0	46.2
27	63	M	2.14	43.0	Early	7.39	65.8	47.7
28	56	M	2.38	47.1	Moderate	7.37	62.3	47.0
29	39	F	1.87	40.0	None	7.41	56.4	39.0
Mean values						$7.38 \pm 0.005\dagger$	$59.0 \pm 0.5$	$44.6 \pm 0.5$
Coefficient of variation						0.54	6.8	8.7

\* Determined by Newcomer's method

† Probable error of the means

46.4 mm. From the data of Earle and Cullen the normal carbon dioxide tension of the venous plasma was found to vary from 37 to 58 mm.

18 Woodward, G. E., Schoonover, J. W., Fry, E. G., Torrance, E. G., and McDonald, E. The Hydrogen-Ion Concentration of the Blood in Untreated Cancer Cases and Its Relation to Prognosis, *J. Lab. & Clin. Med.* **16**: 704 (April) 1931.

19 Earle, I. P., and Cullen, G. E. Studies of the Acid-Base Condition of Blood. I. Normal Variation in  $p_H$  and  $CO_2$  Content of Blood Sera, *J. Biol. Chem.* **83**: 539 (Sept.) 1929.

*Subjects with Pernicious Anemia*—In table 2 are listed the results of the determinations of the  $p_H$  and the carbon dioxide content of the venous plasma in twenty-nine patients with pernicious anemia. Each of the patients was known to possess true achylia, and none had received hydrochloric acid for at least seven days prior to the analysis.

TABLE 3—*The Mean  $p_H$ , Carbon Dioxide Content and Carbon Dioxide Tension of the Venous Plasma in Normal Subjects and in Various Groups of Patients with Pernicious Anemia, Divided According to Severity of Clinical Symptoms and to Treatment with Hydrochloric Acid*

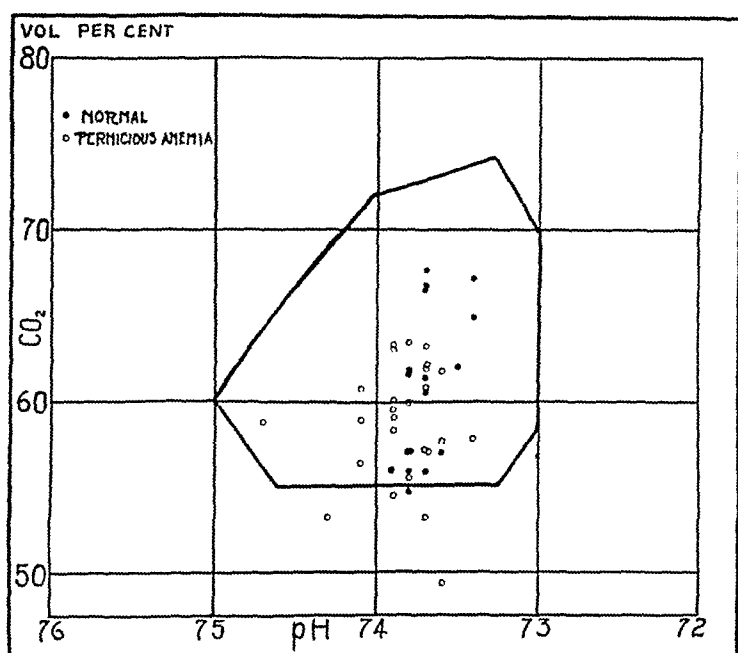
	Num ber of Sub jects	$p_H$		Carbon Dioxide Con tent, Vols per Cent		Carbon Dioxide Tension, Mm	
		Mean Value	Coeffi cient of Varia tion	Mean Value	Coeffi cient of Varia tion	Mean Value	Coeffi cient of Varia tion
I Normal subjects	16	7.37 $\pm$ 0.003*	0.2	61.5 $\pm$ 0.84	7.3	46.4 $\pm$ 0.82	9.5
II Patients with pernicious anemia							
A With early or no demonstrable involvement of the central nervous system	12	7.40 $\pm$ 0.005	0.4	58.2 $\pm$ 0.57	5.0	41.3 $\pm$ 0.68	8.3
B With from moderate to advanced involvement of the central nervous system	17	7.37 $\pm$ 0.004	0.3	58.9 $\pm$ 0.72	6.3	44.5 $\pm$ 0.61	7.0
C With red blood cell counts above 3,000,000	22	7.38 $\pm$ 0.003	0.3	58.4 $\pm$ 0.49	5.8	42.9 $\pm$ 0.45	7.2
D With red blood cell counts below 3,000,000	7	7.39 $\pm$ 0.012	0.6	60.0 $\pm$ 0.77	5.0	44.1 $\pm$ 1.21	10.7
E Receiving from 6 to 10 cc of 10 per cent hydrochloric acid daily	5	7.39 $\pm$ 0.027	1.2	57.4 $\pm$ 1.1	6.4	40.8 $\pm$ 0.86	7.0
F Patients in group E after one week's suspension of treatment with 10 per cent hydrochloric acid	5	7.37 $\pm$ 0.003	0.2	59.8 $\pm$ 0.74	4.0	44.4 $\pm$ 0.58	4.2
G All patients	29	7.38 $\pm$ 0.005	0.5	59.0 $\pm$ 0.5	6.3	44.6 $\pm$ 0.5	8.7

\* Probable error of the mean

The range of the  $p_H$  in this group was from 7.30 to 7.47, the mean value approximating 7.38. The total carbon dioxide content of the venous plasma varied between 53.3 and 65.8 volumes per cent, averaging approximately 59 volumes per cent. The calculated carbon dioxide tension was found to lie between 35.7 and 47.8 mm, with a mean value of approximately 44.6 mm.

In table 3 are recorded the mean values for the  $p_H$  and for the carbon dioxide content of the patients with pernicious anemia, grouped according to the hematologic and the neurologic status of the patient at the time of the analysis. There are included in this table the results obtained with a series of patients who had received daily from 6 to 10 cc of a 10 per cent solution of hydrochloric acid orally and the mean values for the same patients following suspension of the treatment for one week.

The data recorded in tables 1 and 2 are plotted in the chart, and the relation of the plotted points to the normal area published by Austin and Cullen<sup>20</sup> is shown.



Data recorded in tables 1 and 2 plotted according to the normal area of Austin and Cullen<sup>20</sup>. In the diagram, solid dots represent values for normal subjects, hollow dots, those for patients with pernicious anemia.

#### COMMENT

It is evident that there was no sharp variation from the normal acid-base equilibrium in the great majority of patients with pernicious anemia studied. This fact is clearly shown in the chart, in which the data for the normal subjects and for the patients with anemia are plotted together. However, it may be pointed out that there is an apparent tendency toward a deficit of alkali in pernicious anemia if the carbon dioxide content of the venous plasma is accepted as a com-

<sup>20</sup> Austin, J. H., and Cullen, G. E. Hydrogen-Ion Concentration of the Blood in Health and Disease, *Medicine* 4: 275 (Aug.) 1925.



parative measure of the alkali reserve. All of the subjects evidencing a markedly diminished carbon dioxide content are seen to be patients with pernicious anemia. In spite of this tendency, there was found no true acidosis in the sense of a decreased hydrogen ion concentration of the blood. Indeed, in a large number of the patients with pernicious anemia the blood was found to possess a slightly alkaline reaction as compared to that of the group of normal subjects.

No generalizations can justly be made in regard to either the reaction of the blood or the alkali reserve in pernicious anemia on the basis of this investigation, as is clear from a study of the mean values. The differences between the mean  $p_H$ , the total carbon dioxide content and the carbon dioxide tension of the plasma in the normal subjects and the values in the patients with pernicious anemia were, as a group, too slight to be significant. It is interesting to note, however, that the variation in the  $p_H$  was more than twice as great among the patients with pernicious anemia as among the normal subjects, whereas the variations in the carbon dioxide content and the carbon dioxide tension were approximately the same in the two groups.

Grouping the patients with pernicious anemia according to the clinical status yielded interesting results. These data are presented in table 3. It is seen that in the patients with early or no demonstrable changes in the cord, the reaction of the blood, as expressed by the  $p_H$ , was 0.03 units higher, on an average, and the carbon dioxide tension slightly lower, than in the patients with from a moderate to an advanced degree of involvement of the central nervous system. It may be said, then, that alkalosis is not a significant factor in the occurrence of paresthesias in pernicious anemia. No notable differences are to be found due to, or accompanying, the changes in the red blood cell count. Since no appreciable changes were found in the  $p_H$  or the carbon dioxide content of the venous blood following the administration of the specified amount of hydrochloric acid, it cannot be said that the therapeutic value of its administration, such as the relief of gastrointestinal symptoms, is attributable to changes in the acid-base equilibrium.

#### SUMMARY

The  $p_H$  and the carbon dioxide content of the venous plasma were determined in twenty-nine patients with pernicious anemia and in sixteen normal persons.

The results suggest that the condition of the acid-base equilibrium in pernicious anemia is independent of the clinical status and is essentially normal, although there is an apparent tendency toward alkalosis and a deficit of alkali.

Of possible significance is the variation of the  $p_H$  over a range which was twice as broad in the patients with pernicious anemia as in the series of normal subjects

The daily administration of from 6 to 10 cc of a 10 per cent solution of hydrochloric acid produced no appreciable changes in the acid-base equilibrium of the blood in the patients with pernicious anemia

# DIETS LOW IN CALORIES CONTAINING VARYING AMOUNTS OF PROTEIN

THEIR EFFECT ON LOSS IN WEIGHT AND ON THE METABOLIC RATE  
IN OBESE PATIENTS

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AND  
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CHICAGO

In a previous communication,<sup>1</sup> were reported the results of studies of nitrogen excretion in obese patients on diets low in calories, containing varying amounts of protein. It was noted that a negative nitrogen balance was unusual in patients on diets containing 90 Gm of protein, and that the loss of nitrogen on an intake of from 13 to 14 Gm of protein was not significant. The general conclusion reached was that the fat constitutes a mobile supply of energy which is so easily requisitioned that starvation sequelae do not develop, provided carbohydrate is furnished for antiketogenesis and protein for the "wear and tear quota."

In this paper a study of the effect of such diets on the rate of loss in weight and on the metabolic rate is reported. The periods of observation were sufficient to obviate minor variations in weight due to water retention, and thus to establish any variation observed as significant.

## METHODS

The management of the experiment has been previously described. The patients were weighed each morning under standard conditions. The metabolic rate was determined once a week by the oxygen consumption method, using a McKesson machine.

## RESULTS

*Loss of Weight*—The great stumbling-block in the studies of reduction in weight in the obese has been the absence of an accurate measure of the energy expended and the consequent inability to set up a balance sheet covering the exchange of energy. Benedict and Root<sup>2</sup> have shown

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From the Department of Medicine of the University of Illinois College of Medicine

1 Keeton, Robert W, and Bone, Dorothy D. Excretion of Nitrogen by Obese Patients on Diets Low in Calories, Containing Varying Amounts of Protein, *Arch Int Med* **51** 890 (June) 1933

2 Benedict, F G, and Root, H F. Insensible Perspiration. Its Relations to Human Physiology and Pathology, *Arch Int Med* **38** 1 (July) 1926

that the basal metabolic rate may be estimated from the insensible perspiration Newburgh and Johnston<sup>3</sup> extended this method to the measurement of the total production of heat by establishing precautions to avoid undue cooling of the body, sweating and the performance of work Using this method, they concluded that loss of weight can be accurately predicted, and that the obese patient subjected to a diet inadequate in calories loses weight quantitatively

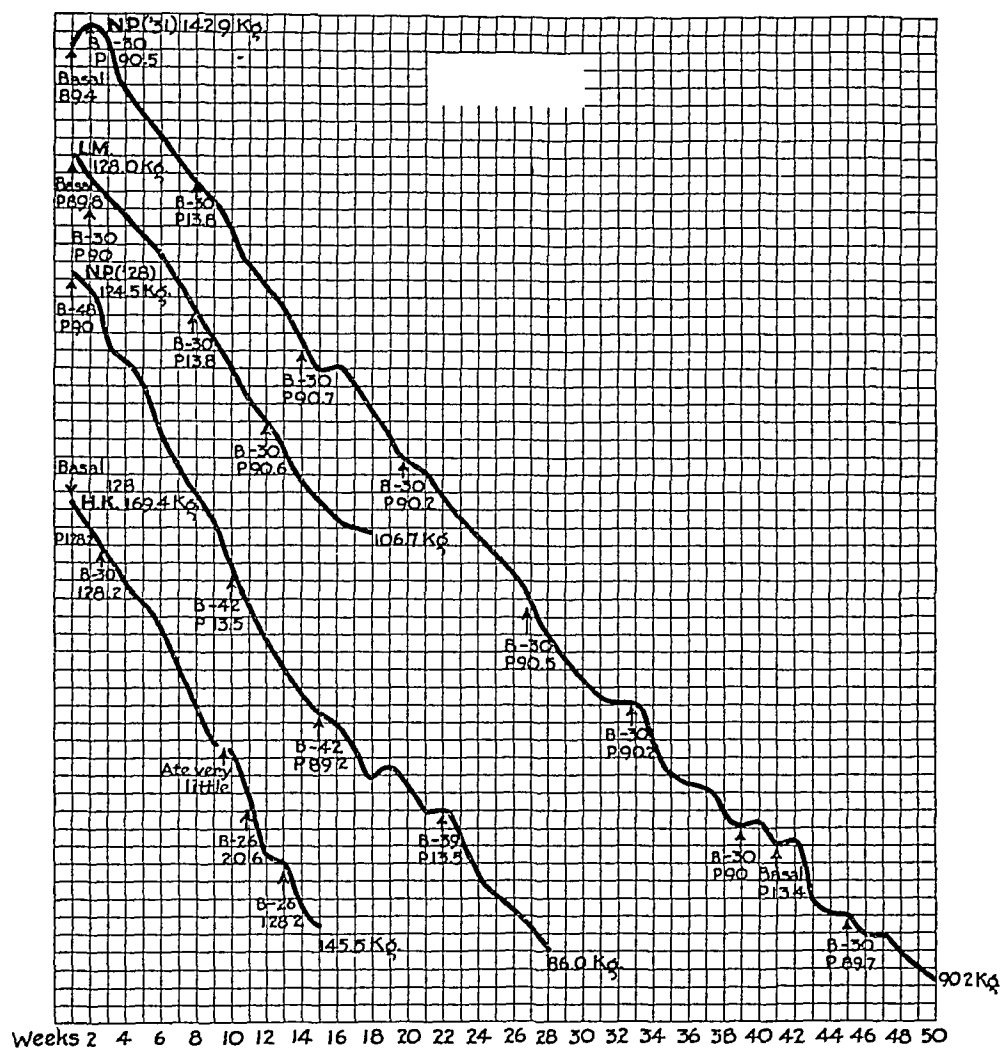


Chart 1—Curves showing loss of weight, expressed in kilograms, during a period of several weeks, in four obese patients receiving diets low in calories containing shifting amounts of proteins varying approximately from 90 to 13 Gm and vice versa Each division along the ordinate represents 1 Kg

Our patients were confined to the hospital but were allowed to be out of bed and around the wards They usually took a period of rest in the afternoon The activity was classified as "ambulatory" However, there were individual differences in the activity, large in some

3 Johnston, Margaret W, and Newburgh, L H Determination of Total Heat Eliminated by Human Being, *J Clin Investigation* 8 147, 1930 Newburgh, L H, and Johnston, Margaret W The Nature of Obesity, *ibid* 8 197, 1930

cases, so that the expenditure of energy in one patient could not be compared with that in another. It is to be noted that the diets are designated as "basal minus 30 per cent" or "basal minus 48 per cent." The basal requirements are based on the observed surface area rather than on the ideal surface area, as suggested by Strang and Evans<sup>4</sup>. Since the fat is to be regarded as storage material and is presumably not a part of the active metabolizing tissues, they thought it justifiable to discount its effect on the metabolism. However, the fat does increase the surface area, and it has been generally accepted that the metabolism varies with the surface area. A mathematical convention, therefore,

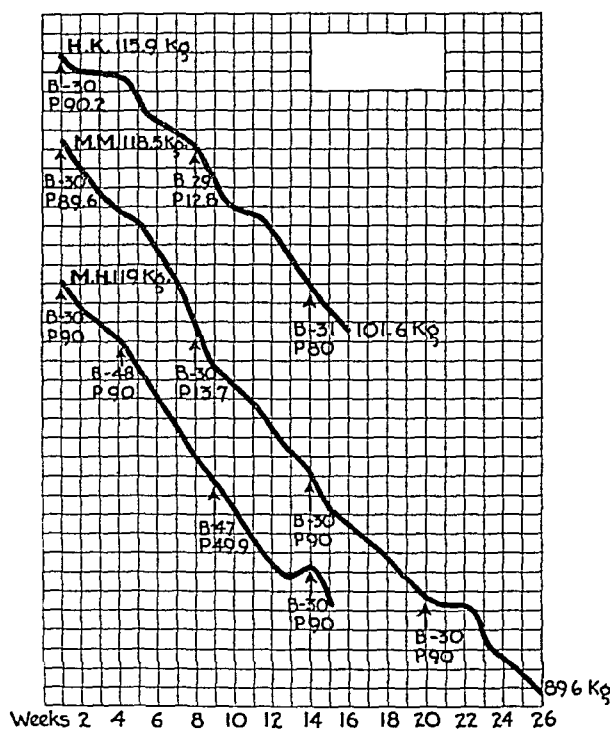


Chart 2—Curves showing loss of weight in three obese subjects under conditions similar to those indicated in chart 1. Each division along the ordinate represents 1 Kg.

which ignores this increment in surface area due to fat does not at present seem justified.

In charts 1, 2 and 3, the weights of the patients are plotted at weekly intervals. The base line has been shifted so as to group the weight curves for comparison. Each division along the ordinate represents 1 Kg., and each division along the abscissa one week. The caloric value of the diet and the quantity of protein expressed in grams are also indicated.

In five of the experiments (NP, 1931 and LM, chart 1, HK and MM, chart 2, and SC, chart 3), the diets consisted of basal minus 30

<sup>4</sup> Strang, James M., and Evans, Frank A. The Energy Exchange in Obesity, *J. Clin. Investigation* 6: 277, 1928.

per cent calories In the two remaining experiments (NP, 1928, chart 1, and MH, chart 2), the reduction in calories was somewhat greater, but the experimental periods are comparable With each change of diet, the basal requirement was recalculated and adjusted to the new surface area, but there were no further adjustments during the period It was believed that this plan subjected the patient continuously to the same quantitative degree of undernutrition and allowed any effect arising from the shifting of the protein to manifest itself

It is to be noted that the slopes of the weight curve do not change significantly when the quantity of protein is shifted from 90 to 13 Gm, or vice versa

The same result is shown when the data are treated differently, as in the table Here the daily loss in weight expressed in grams is computed for each type of diet If the loss appeared greater on the high protein diet, it is charted in the last column as H P, if greater on the low protein diet, as L P By reference to this column, it is seen that

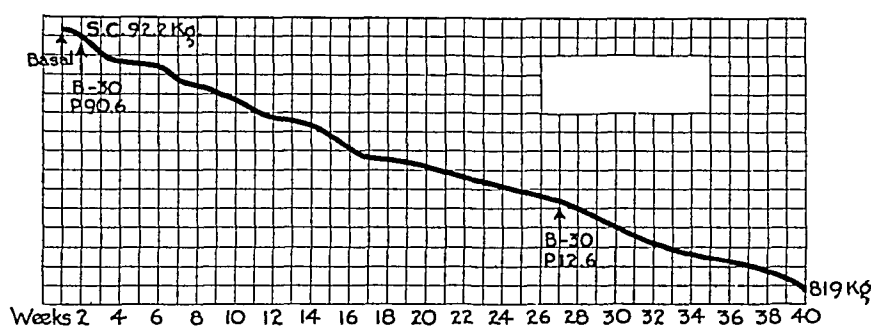


Chart 3—Curve showing loss of weight in one obese patient under conditions similar to those indicated in charts 1 and 2 Each division along the ordinate represents 1 Kg

in two of the patients, the loss was greater on a high protein diet, and in four, on a low protein diet, in two patients the loss was the same on the two diets, and for one the results were inconclusive In other words, there is no correlation in the data with reference to changes in the amount of protein

Similar observations have been previously reported in the case of hogs<sup>5</sup> placed on submaintenance diets with varying amounts of protein The loss in weight paralleled the reduction in calories and was independent of changes in the protein content of the diet

It is also to be noted that with the same proportionate reduction in the diet, the loss in weight seemed to be greater in the more obese patients The explanation of this loss is not clear, and this conclusion

<sup>5</sup> Keeton, Robert W, MacKenzie, H, Olson, S, and Pickens, L The Influence of Varying Amounts of Carbohydrate, Fat, Protein and Water on the Weight Loss of Hogs in Undernutrition, *Am J Physiol* **97** 473 (June) 1931

should not be stressed, because of the necessity of comparing the loss of weight in one subject with that in another in the absence of a measure of their activity

The question naturally arises as to whether these experiments throw any light on the vexed problem of the specific dynamic action of food in the obese, a question which has led to many diverse studies and conflicting opinions<sup>6</sup> Lusk<sup>7</sup> noted that carbohydrates and fats do not

*Loss in Weight Under High and Low Protein Diets of Low Caloric Value in Nine Obese Patients*

Patient	Name	Calories*	Protein	Weight Loss in Gm per Day on		Diet Producing Greater Loss†
				High Protein Diet	Low Protein Diet	
1	S C	B 30%	14 5	120 0 Gm for 34 days	113 6 Gm for 42 days	Equal
		B 30%	2 11	105 4 Gm for 43 days		
		B 30%	14 5			
2	H H	B 30%	14 4	120 2 Gm for 22 days	70 9 Gm for 25 days	H P
		B 25%	14 4	113 6 Gm for 29 days		
		B 42%	2 24			
3	M H	B 30%	14 5	159 1 Gm for 30 days	101 3 Gm for 38 days	H P
		B 48%	14 006	194 5 Gm for 35 days		
		B 42%				
4	H K	B 30%	20 46	282 8 Gm for 45 days	470 8 Gm for 14 days‡	L P
		B 26%	2 016			
5	H K	B 30%	14 4	107 9 Gm for 59 days	165 3 Gm for 44 days	L P
		B 29%	2 048			
6	N P	B 48%	14 4	231 3 Gm for 72 days	235 9 Gm for 31 days	L P
		B 42%	2 016			
		B 42%	14 27	113 6 Gm for 54 days	181 8 Gm for 45 days	
		B 39%	2 016			
7	N P	B 30%	14 48	216 4 Gm for 42 days	221 8 Gm for 42 days	Equal
		B 30%	2 201	129 86 Gm for 42 days		
		B 30%	14 512			
8	M M	B 30%	14 432	200 2 Gm for 42 days	183 98 Gm for 42 days	Equal
		B 30%	2 192	140 7 Gm for 42 days		
		B 30%	14 368			
9	L M	B 30%	14 51	178 6 Gm for 42 days	211 03 Gm for 28 days	L P
		B 30%	2 201	135 3 Gm for 42 days		
		B 30%	14 5			

\* B represents the basal caloric requirement

† H P represents a high protein diet, L P, a low protein diet

‡ Experiment was of short duration

6 Strous, S, Saunders, A D, and Wang, C C Specific Dynamic Action of Food, Arch Int Med **34** 573 (Oct) 1924 Plaut, R Gaswechseluntersuchungen bei Feltsucht und Hypophysiserkrankungen, Deutsches Arch f klin Med **139** 285, 1922, Gaswechseluntersuchungen bei Feltsucht, *ibid* **142** 266, 1923 Du Bois, E F, Spencer, H J, McClellan, W S, and Falk, E The Specific Dynamic Action of Protein in the Obese, J Clin Investigation **7** 499, 1929 Lauter, S Zur Genese der Feltsucht, Deutsches Arch f klin Med **150** 315, 1926 Strang, J M, and McClugage The Specific Dynamic Action of Food in Abnormal States of Nutrition, Am J M Sc **182** 47, 1931 Johnston, Margaret W The Specific Dynamic Response to Protein of Individual Suffering from Disease of the Hypophysis, J Clin Investigation **11** 437, 1932

7 Lusk, G The Specific Dynamic Action of Various Food Factors, Medicine **1** 311, 1922

cause an increase in the metabolism, unless there is a plethora of molecules in excess of the immediate energy requirements. Thus in a fasting dog with a low respiratory quotient, the value of the quotient was raised to 1 by the intake of a certain number of grams of dextrose, and yet no elevation of the metabolism appeared. With a further increase in the dextrose the specific dynamic action then appeared, and the metabolism was increased. On the high protein diets these patients received between 1,000 and 1,200 calories with an intake of protein of 90 Gm, of carbohydrate, of from 80 to 90 Gm, and of fat from 30 to 50 Gm. With a lowering of the amount of protein to from 13 to 14 Gm, the carbohydrate intake reached a value of from 150 to 160 Gm. It is to be remembered that these diets were always inadequate in calories, approximately 45 per cent below the actual energy expended. One concludes, therefore, that no stimulating effect is to be expected from the carbohydrate or the fat. In the case of protein, the story seems to be different. Here the stimulating effect is due to the intermediary products of the oxidation of certain amino-acids (Lusk), and this effect seems to be superimposed on the energy requirements for work. Such a stimulation does not occur in the absence of the liver (Mann and his co-workers<sup>8</sup>), in fact, 85 per cent of the heat produced originates within the liver (Dock<sup>9</sup>).

Under the conditions of our experiments, if the intake of 90 Gm of protein stimulated the metabolism more than that of 13 Gm, it was not reflected in the loss of weight. This seems to furnish evidence in favor of the lowering of the specific dynamic action of protein in the obese. However, in this connection it should be recalled that all of these patients were storing nitrogen on a diet containing 90 Gm of protein, and on one containing 13 Gm were not losing significant quantities of nitrogen. It seems justifiable to assume that such a storage represented additions to the deposit of nitrogen.

Lusk<sup>7</sup> showed that protein which is used for purposes of replacement did not cause a specific stimulation, and McCann<sup>10</sup> demonstrated that the specific dynamic action of protein was greatly reduced after a fast of eight days. In his patient the nitrogen excretion was not aug-

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8 Mann, F. C., Wilhelmj, C. M., and Bollman, J. L. The Specific Dynamic Action of Glycocoll and Alanine with Special Reference to the Dehep- atized Animal, *Am J Physiol* **81** 496, 1927. The effect of Removal of the Liver on the Specific Dynamic Action of Amino-Acids Administered Intravenously, *ibid* **87** 497, 1928.

9 Dock, William. The Relative Increase in Metabolism of the Liver and Other Tissues During Protein Metabolism in the Rat, *Am J Physiol* **97** 117, 1931.

10 McCann, W. S. An Observation of the Effect of a Protein Meal Given to a Man at the End of an Eight Day Fast, *Proc Soc Exper Biol & Med* **17** 173, 1920.



mented by the ingestion at a single meal of 350 Gm of meat, the equivalent of 87.5 Gm of protein. It is highly probable, therefore, that in our experiments the state of the subject was such that the foods given did not furnish an adequate stimulus for initiating specific dynamic action.

*Metabolic Rate*—In chart 4, the metabolic rates estimated at weekly intervals are plotted. Each division in the abscissa represents a period of one week, and each division in the ordinate, a variation of 10 per cent in the metabolism. The zone of cross hatching represents a variation of 10 per cent above and below the zero line, which is usually considered the normal allowable variation.

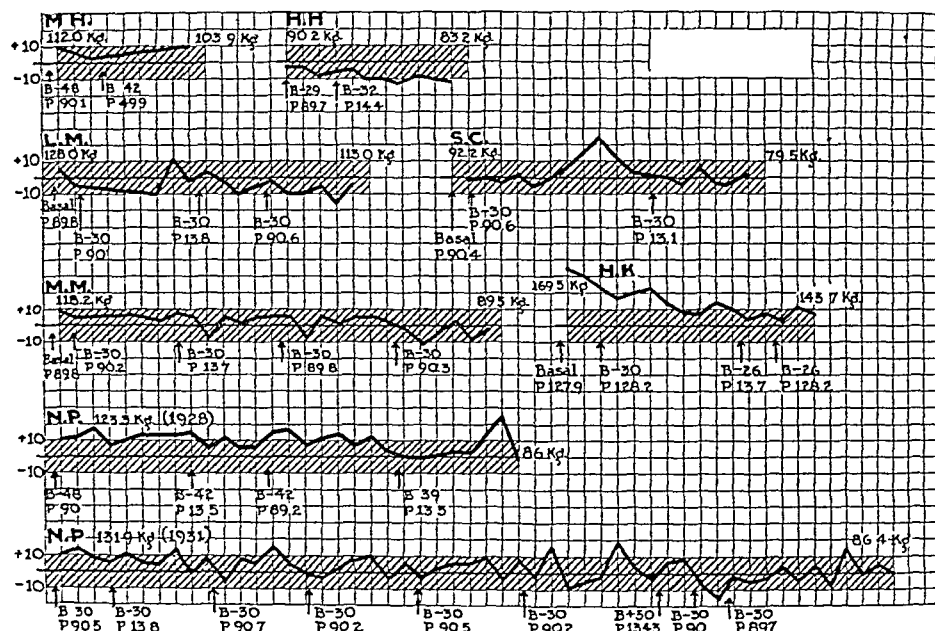


Chart 4—Graphic representation of basal metabolic rates determined at weekly intervals over periods of from eight to fifty-three weeks for the eight obese patients whose weight curves are shown in charts 1, 2 and 3. The curves for the weekly determinations of the rate are indicated by heavy, solid lines, the limits of normal variation in the basal metabolic rate, by cross-hatched areas.

The shortest period over which metabolic rates were determined was eight weeks, in the case of M. H., a patient confined to bed. The longest period was fifty-three weeks. These periods certainly gave abundant opportunities for changes in the rate which might result from the experimental procedures to manifest themselves. It should be mentioned that H. K., a short, obese, thick-chested, apprehensive woman, had considerable difficulty in learning to cooperate in the test. On several occasions at the beginning, it was necessary to discard the test as obviously incorrect and repeat it on succeeding days. With the exception of the experiments on this patient, one may conclude that the metabolic rate

does not decrease in an obese patient undergoing reduction in weight by the restriction of the diet. It may be further observed that the metabolic rate is not decreased when, in addition to the reduction in calories, the protein in the diet is lowered so as to induce "specific nitrogen hunger" and establish the excretion of a "nitrogen minimum" in the urine.

Strang and Evans<sup>4</sup> obtained the same results although, as previously mentioned, their patients lost somewhat less weight. However, they preferred to estimate the metabolism on the basis of the ideal rather than the observed surface area. With this method of calculation, they concluded that the metabolism of the obese patient is above the normal and that during reduction in weight it returns to normal. According to this view, the reduction process is responsible for the lowering of the metabolism.

In the normal subject, as reported by Benedict and his associates<sup>11</sup> and as discussed by Lusk,<sup>12</sup> the metabolic rate decreases approximately 30 per cent following the sudden reduction of calories. Lusk summarized the situation as follows: "A minimal metabolic rate, which is two-thirds that of the normal basal metabolism, seems to be easy to establish and affords another of those striking 'factors of safety' of which Meltzer has so cogently written."

Anderson and Lusk<sup>13</sup> have made observations on the influence of a normal maintenance diet on the basal metabolism of a dog before and after fasting. They noted that after the metabolism had been reduced by fasting, a maintenance diet did not restore it to normal the following day, and they concluded that evidently the condition of the body, and not a large influx of food on the day previous, determines the height of the basal metabolism.

Deuel, Sandiford, Sandiford and Boothby<sup>14</sup> reported an experiment on a normal subject, H. J. D., placed on a protein-free diet of sub-maintenance caloric value. This subject, although labeled "normal," may have been slightly overweight (15 per cent). However, his metabolic rate fell during the experiment from — 9 per cent to — 20 per

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11 Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M. *Human Vitality and Efficiency Under Prolonged Restricted Diet*, Washington, D. C., Carnegie Institution of Washington, 1919, pub. 280.

12 Lusk, G. *The Physiological Effects of Undernutrition*, *Physiol. Rev.* **1**, 523, 1921.

13 Anderson, R. J., and Lusk, G. *Animal Colorimetry. XIII. Inter-relation Between Diet and Body Condition and the Energy Production During Mechanical Work*, *J. Biol. Chem.* **32**:421, 1917, cited by Lusk.<sup>12</sup>

14 Deuel, Harry J., Jr., Sandiford, Irene, Sandiford, Kathleen, and Boothby, Walter M. *The Effect of Sixty-Three Days of a Protein-Free Diet on the Nitrogen Partition Products in the Urine and on the Heat Production*, *J. Biol. Chem.* **76**: 391, 1928.

cent It may be suggested that this decrease in the rate was due to the absence of protein from his diet This explanation is rendered improbable by the occurrence of a similar decrease in patients on diets containing maintenance quantities of protein It has also been noted by Allen and Du Bois<sup>15</sup> that subnormal weight is associated with a lower metabolism than normal weight Again we quote from Lusk, who stated that there is not only a mechanism for the maintenance of a minimum of nitrogen which protects life from destruction, but, in the normal person, a biologic adaptation to a lowered energy intake, which prevents the exhaustion of the reserves of body fat

In the obese person, the large stores of fat are so readily available for energy production that the body stores of nitrogen are preserved, even when the individual is faced with specific nitrogen hunger These stores of fat also prevent the lowering of the metabolic rate which in the normal person is produced by a shortage of calories There is no such shortage in the obese

#### CONCLUSIONS

1 Obese patients confined to the hospital, allowed the freedom of the ward and receiving diets of from basal minus 30 per cent to basal minus 48 per cent calories lose weight equally well when these diets contain 90 or 13 Gm of protein Such diets supply approximately 55 per cent of their actual caloric requirement The remainder is secured from the body fat

2 Under the conditions of the experiment there is negligible stimulation of the metabolism by the food This experiment throws no light on the specific dynamic action of foods in the obese

3 The metabolic rate is not lowered by a dietary undernutrition of this degree of severity lasting for from eight to fifty-three weeks

4 The metabolic rate is not lowered by the same degree of dietary undernutrition when it is associated with specific nitrogen hunger

5 The supplies of stored fat not only protect the body from loss of nitrogen but they also prevent the conservation of energy seen in the normal person when subjected to undernutrition

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15 Allen, F M, and Du Bois, E F Clinical Calorimetry XVII Metabolism and Treatment in Diabetes, Arch Int Med **17** 1010 (June) 1916

# PEPTIC ULCER

NATURE AND TREATMENT BASED ON A STUDY OF ONE THOUSAND,  
FOUR HUNDRED AND THIRTY-FIVE CASES

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AND

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Peptic ulcer continues to provoke voluminous and diverse opinions each year in respect to both its nature and its treatment. No one can read more than a few of those opinions without bewilderment, and this confusion serves to perpetuate the admittedly unsatisfactory management of the condition. Only a careful and prolonged observation of many patients helps to distinguish fact from theory. We are emboldened to restate our views because time has confirmed them and because we believe that they offer the best available approach to the handling of the individual cases.

Our first report,<sup>1</sup> published in 1929, was a statistical survey of 556 cases of ulcer of the stomach and duodenum. For our present purpose all our cases, up to Jan 1, 1932, including the original series, have been analyzed in the same manner. There are 1,435 cases (table 1), and wherever possible the figures are relegated to tables. We wish to discuss the problem generally rather than to substitute new figures for old.

## NATURE OF THE DISEASE

The fundamental cause of peptic ulcer remains unknown in spite of an enormous amount of investigation. Experimentally it is possible to produce ulcer—at least acute ulcer—by a great number of unrelated methods, but it is not clear whether any one of these methods is the sole cause of all the chronic lesions found in man. The chief theories—vascular (Virchow), mechanical (Aschoff), constitutional (Draper), infectious (Rosenow) and neurogenic (von Bergmann)—are well known and have been reviewed recently by Rivers.<sup>2</sup> No one of these theories seems to fit all the instances of the disease, though various combinations of the conditions they analyze may occur.

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From the Medical Clinic of the Peter Bent Brigham Hospital

1 Emery, E S, Jr, and Monroe, R T. Peptic Ulcer. A Study of Five Hundred and Fifty-Six Cases, *Arch Int Med* **43** 846 (June) 1929

2 Rivers, A B. Clinical Consideration of the Etiology of Peptic Ulcer, *Arch Int Med* **53** 97 (Jan) 1934

*The Acid Factor*—Certain characteristics of the disease are universally agreed on. One of these is that it occurs only in the regions of the gastro-intestinal tract which are in contact with hydrochloric acid. Ulcer is found in the stomach, in the beginning of the duodenum, in the esophagus just above the cardiac sphincter and in the jejunum when it has been anastomosed to the stomach by some surgical procedure. Lindau<sup>3</sup> has pointed out that an ulcer which occurs in a Meckel's diverticulum or in the esophagus are associated with aberrant gastric tissue. Palmer's<sup>4</sup> studies on the clinical relationship of free hydrochloric acid to active ulcer are in entire accord with our experience. We have observed no instance in which an ulcer gave characteristic symptoms in the absence of free hydrochloric acid. Two patients, one with pernicious anemia and the other with osteitis deformans and achlorhydria, even after the administration of histamine had typical roentgenologic appearances of duodenal ulcer but did not have ulcer distress, there was no opportunity to determine whether they had true ulcers or not.

TABLE 1—*General Survey of the Cases Reported in This Study*\*

Total number of patients	1,435
Age at time of first observation	14-80 years
Average age at onset of ulcer symptoms	35 years
Ratio of males to females	55:1
Occupation: Manual labor	703
Clerical work	442
Housework	290
Location of ulcer: Duodenal	1,167
Gastric	215
Gastric and duodenal	53

\* All the patients entering the wards or outpatient department of the Peter Bent Brigham Hospital from its opening in 1913 to Jan. 1, 1932, are included.

From the clinical observation it is difficult to believe that the acid factor is the only one which operates to produce the localized destruction of mucous membrane that is called peptic ulcer. Until further studies throw more light on the etiologic factors responsible for the syndrome one can do no more than obtain a clear understanding of the behavior of the disease.

*Chronicity of Peptic Ulcer*—In 1929 we<sup>1</sup> stated "All evidence points to the fact that ulcer is a chronic disease and that all the present methods of treatment are merely palliative. Cure probably is rare." The data pointing to the chronicity of the disease are now so complete that it is impossible to doubt their accuracy. This becomes evident

3 Lindau, A., and Wulff, H. The Peptic Genesis of Gastric and Duodenal Ulcers, *Surg., Gynec. & Obst.* **53**: 621 (Nov.) 1931.

4 Palmer, W. L. The Mechanism of Pain in Gastric and Duodenal Ulcers. I. Achlorhydria, *Arch. Int. Med.* **38**: 603 (Nov.) 1926.

from (1) an analysis of the course of the disease, (2) the results of treatment and (3) roentgenologic and histologic studies

Brown<sup>5</sup> stated that following the Sippy treatment 49.5 per cent of patients were cured and 16.7 per cent greatly improved. Stowell<sup>6</sup> noted that one half of the patients discharged from a London hospital suffered a relapse in succeeding years. Fremont-Smith and McIver<sup>7</sup> found that in only 66 per cent of their surgical cases did symptoms disappear entirely after several years. Walton<sup>8</sup> had immediate and satisfactory results in 67 per cent of his male and in 76 per cent of his female patients, but after some years only 20 per cent of the men and 40 per cent of the women had been relieved. In 1,350 cases in which operation for peptic ulcer was performed in his clinic, Wanke<sup>9</sup> found that 110 patients had to have a second operation for a recurrence of symptoms. Thirty-seven per cent of Forsyth's<sup>10</sup> patients suffered a relapse from one to seven times in from one to twelve years. Lahey<sup>11</sup> found that the results of surgical and of medical treatment were practically the same at the end of five years and that at that time treatment had been successful in only slightly more than 50 per cent of the cases. Alvarez<sup>12</sup> and Hurst<sup>13</sup> were impressed with the chronicity of the disease, and Brooks<sup>14</sup> said "Until the cause of peptic ulcer has been definitely demonstrated we should not speak confidently of the cure of the condition but rather of mitigation of certain of its signs and symptoms. We [referring to physicians and surgeons] are neither of us curing the disease."

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5 Brown, R. C. Ulcer of the Stomach and Duodenum, in Christian, Henry A. and Mackenzie, J. Oxford Medicine, New York, Oxford University Press, 1931, vol. 3, chap. 3, p. 172.

6 Stowell, in Kemp, R. C. Diseases of the Stomach, Intestine and Pancreas, ed. 3, Philadelphia, W. B. Saunders Company, 1917, p. 295.

7 Fremont-Smith, M., and McIver, M. A. Late Results of Surgical Treatment of Peptic Ulcer Based on a Study of Six Hundred and Seventy-Eight Cases, *Am. J. M. Sc.* **177** 33 (Jan.) 1929.

8 Walton, A. J. The Results of Surgical Treatment of Gastric and Duodenal Ulcer, *Brit. M. J.* **2** 784 (Nov. 3) 1928.

9 Wanke, R. Operierte chirurgische Misserfolge des Ulcusleidens und der chronischen Gastritis, *Deutsche Ztschr. f. Chir.* **220** 263 (Nov.) 1929.

10 Forsyth, D. Duodenal Ulcer Among Medical Men. A Comparison of the Results of Surgical and Medical Treatment, *Brit. M. J.* **1** 780 (May 3) 1924.

11 Lahey, F. H. The Management of Peptic Ulcer, *New England J. Med.* **205** 321 (Aug. 13) 1931.

12 Alvarez, W. C. What Is the Risk of Insuring Applicants with Peptic Ulcer? *Am. J. M. Sc.* **178** 777 (Dec.) 1929.

13 Hurst, A. F. Recent Advances in the Treatment of Gastric Diseases, *Brit. M. J.* **2** 779 (Nov. 3) 1928.

14 Brooks, H. The Selection of Cases for Medical or Surgical Treatment in Gastric and Duodenal Ulcer. *Boston M. & S. J.* **198** 339 (April 5) 1928.

The untreated peptic ulcer pursues an up and down course for many years. The symptoms fluctuate, with spontaneous remissions and relapses. This has long been recognized as a cardinal point in the diagnosis of the disease. The interval between attacks may vary from weeks to months or years. Three patients in our series stated that for twenty years they had been without trouble of any sort. There are also many persons with peptic ulcer whose symptoms are so mild or so infrequent that they never seek medical aid. The ulcer is found incidentally either at necropsy or in the course of investigation for some other reason. Persistence is a quality which all attribute to ulcer before treatment. This is shown in the designation "chronic peptic ulcer." It is seen in the long duration of symptoms before patients apply for relief, which averages seven years in our series. It is implied in the old surgical aphorism, "Don't operate until after seven medical cures." It has taken a long time to show that it is just as true after all forms of treatment have been utilized.

Finally, roentgenologic studies furnish indisputable proof of the chronicity of ulcer, as we<sup>15</sup> have pointed out elsewhere. Crohn<sup>16</sup> and his co-workers have demonstrated the temporary nature of the disappearance of a crater in the stomach. They have treated gastric ulcers until the crater has disappeared as shown by the roentgenograms. Then, when the region was excised at operation the ulcer was found to be healed or in the last stage of healing. However, if operation was delayed until a return of symptoms occurred the ulcer was found to be present. Nicholas and Moncrieff<sup>17</sup> have shown the association between a gastric crater and the presence of symptoms. By observing patients with the roentgen rays for a long enough time they have been able to show that a spontaneous remission of symptoms is accompanied by a spontaneous disappearance of the crater and that the return of symptoms is associated with a reappearance of the niche. That duodenal ulcers behave in a similar way has been shown in the last three years by Dr. M. C. Sosman at the Peter Bent Brigham Hospital.

Because of all this it becomes evident that treatment must not be directed solely to curing the ulcer. Time alone may do that. It must seek to prevent the appearance of other ulcers, which is called relapse.

*Factors Influencing Relapse*—If one cannot free the patient from the disease it should be helpful to discover how best to fit him to it.

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15 Emery, E. S., Jr., and Monroe, R. T. Peptic Ulcer. The Diagnostic Value of the Roentgen Ray Before and After Treatment, *Am J Roentgenol* 25: 51 (Jan.) 1931.

16 Crohn, B. B., Weiskopf, S., and Aschner, P. W. Life Cycle of Peptic Ulcer, *Arch Int Med* 35: 405 (April) 1925, The Healing of Gastric Ulcers, *ibid* 37: 217 (Feb.) 1926.

17 Nicholas, F. G., and Moncrieff, A. Healing of Gastric Ulcers. Radiological Observations, *Brit M J* 1: 999 (June 4) 1927.

To what are relapses due? We have been interested in this question for the last seven years. Often no cause is assignable, they seem quite spontaneous. But we have been impressed by the frequency with which three factors—fatigue, emotion and infection—seem responsible. Fatigue arising from too long hours of work, exhausting work or a poorly arranged schedule (night work) preceded a relapse in 334 of 1,279 patients that were studied in this regard. Emotional excitement, anger, worry, grief, too much social distraction and the like were the reasons for relapse in 258 cases. Infections, particularly of the upper respiratory tract, were found to precede a relapse in 167 cases. It is striking that only 37 patients believed that indiscretions in diet were the cause. Severe infections, such as pneumonia, rarely seemed to cause ulcer distress. Patients with ulcers require rest in bed and often attention to diet, in other words, some measure of medical treatment which is good for ulcer. It is rather the minor diseases—colds and grip—which do not enforce rest which bother the patient with an ulcer. Such conditions may be concerned in part with the variations in the spring and fall which we have noted and which Hutter<sup>18</sup> has emphasized, but the seasonal incidence of relapses is at times so striking as to cause speculation about some derangement of metabolism.

*Frequency and Duration of Remissions*—Periods of freedom from ulcer distress are an integral feature of the disease, although the frequency and duration of relief vary within wide limits in different patients. Of the 500 patients questioned particularly on this point the remissions seemed definitely spontaneous in 131, vacation gave relief in 5, whereas in the others the remissions were associated with some form of treatment. Experience and the advice of friends and relatives frequently afforded the patients some degree of medical advice without resort to a physician.

While a large number of patients had remissions lasting only months or weeks or for so short a time as almost to escape their attention, it is obvious that the duration varies a great deal. Six patients had remissions lasting up to two years, 95, up to three years, 35, from three to six years, 2, from six to nine years, and 3, for twenty years.

*Prognosis*—Ulcer is rarely a fatal disease. In our series of 1,435 patients, of 161 who died, only 87 (60 per cent) died from ulcer. Hemorrhage was the cause of death in 20, perforation in 28, obstruction in 4 and associated diseases and complications in 35. These cases have been analyzed fully and will be reported on in another article. Our impression is that death from ulcer should be still less common in the future. This is quite different from the experience of a generation ago,

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18 Hutter, K. Etiologic Relation Between Seasonal Variations and Occurrence of Ulcers, *Arch f klin Chir* **151** 651, 1928.



when the disease was regarded as a serious risk. Since that time, however, the situation has changed in several important respects. Then only the severe cases with some complication were recognized. The increasingly frequent use of the roentgenogram now results in earlier diagnosis and in the recognition of mild cases which were formerly classified as cases of hyperacidity. Medical and surgical treatments have been improved, and the indications for each have been more clearly defined.

Moreover, peptic ulcer does not tend to shorten the victim's life. The average age at death in our 87 patients who died of ulcer was 59. This is the life expectancy for the general population. Ulcer is important largely because of the economic risk it entails. It may cause a loss of time from work, alter schedules of living, narrow one's range of

TABLE 2—*Incidence of Complications According to Duration of the Disease in 1,435 Cases of Peptic Ulcer*

Duration of Symptoms, Years	Number of Cases	Percentage with Complications
1	83	38.6
2	103	34.9
3	109	36.6
4	81	39.5
5	98	30.6
6-10	368	48.0
11-15	229	48.0
16-20	156	41.6
21-30	140	58.5
31-40	44	45.4
41-50	22	45.4
51	2	100.0

activity and compel attention to diet and food habits. These restrictions may prove to be blessings in disguise, for they force a person to live within his physical capacity from early middle age onward.

It is also reassuring that in general a peptic ulcer has little tendency to become worse as time goes on. Of 1,012 patients on whom data are available no change in the condition of the ulcer has developed in 872 (86.2 per cent). Obstruction has appeared or increased in 26, hemorrhage occurred in 49 who had not bled previously, pain has increased in 33, perforation resulted in 10, jejunal ulcers, in 20, and an hour-glass contracture, in 2. That the patients in whom the ulcer shows no change are not always those followed for the shortest time is shown in table 2, in which the duration of the ulcer has been determined by adding to the duration of symptoms before treatment the interval from the first to the last visit to the hospital. The surprisingly small change in the incidence of complications with advancing years is apparent. Up to the fifth year complications occurred in about 36 per cent of the cases, thereafter the incidence progressed to about 48 per cent.

We have been unable to find any means for predicting in which patients complications will develop and in which they will not. Some have a hemorrhage or perforation at the onset and live for years with little or no trouble. Others go on for years with only mild distress and then get into trouble. One man of 70 was seen with a duodenal ulcer and moderate symptoms that began at the age of 25, under medical treatment he had a good measure of relief until the age of 75, when prostatic hypertrophy caused urinary obstruction and he had a gross hemorrhage, treatment again helped, and he is still in good condition.

TABLE 3—*Duration of Observation of 1,435 Patients with Peptic Ulcer*

Years	Number of Cases	Percentage
0	177	12.3
To 1 year	242	16.9
1-5	683	47.5
6-10	229	15.9
11-15	85	5.9
16-20	15	1.0
21-25	2	0.1
25+	2	0.1

TABLE 4—*General Summary of the Results of Treatment of 1,435 Patients with Peptic Ulcer\**

	Final Results on All the Patients		Results of Surgical Treatments		Results of Medical Treatments		Results on Untreated Patients	
	No of Patients	Per centage	No of Patients	Per centage	No of Patients	Per- centage	No of Patients	Per- centage
No symptoms	221	17.5	91	19.0	149	13.7	30	23.8
Very few symptoms	411	32.6	93	19.3	397	36.5	11	8.7
Definite improvement	389	30.9	119	24.8	335	30.8	20	15.8
Improvement	65	5.1	39	8.1	69	6.3	5	3.9
No improvement	172	13.6	138	28.7	135	12.5	60	47.6
Totals	1,258		480		1,085		126	
No follow up	177							

\* The final status of the 1,258 patients that were followed is shown in the first column. In the other columns are grouped the results of the main classes of treatment.

#### RESULTS OF TREATMENT

A survey of what has been accomplished by treatment in this group of patients with ulcers should prove helpful in arriving at a decision as to the best way to manage the disease. The average duration of observation is three and nine-tenths years (table 3), but since 23 per cent of the patients have been followed for more than six years, a reasonably long range view is included.

When we estimate carefully the final results of treatment (table 4) we find that in the group which received treatment there are fewer patients without symptoms than among those whose ulcers were not treated, 17.5 per cent had no symptoms as compared to 23.8 per cent

Yet this is exactly what is to be expected from the nature of the disease. The untreated patients form a control group which shows the natural history of ulcer and against which we must measure our efforts to alter its course. They were persons in whom the lesion was seen at necropsy or in life during the course of investigation for other conditions. That such a large proportion of them had never had trouble from their ulcers emphasizes our statement that no treatment has proved to be of curative value. On the other hand, about half of the untreated patients were unimproved, and only in one fourth did care given to other complaints appear to improve the ulcer.

Thirty-two per cent of the patients who received treatment had very few symptoms thereafter. They might reasonably be classified as cured, had not careful personal interviews demonstrated that on occasions they still experienced a mild distress similar to that which they had before.

TABLE 5—*Reasons for Failure in 1,085 Cases of Medical Treatment and 480 Cases of Surgical Treatment*

	Medical Treatment		Surgical Treatment		No Treatment	
	No of Patients	Per centage	No of Patients	Per centage	No of Patients	Per centage
Pain	386	35.5	197	41.0	52	41.4
Hemorrhage	88	8.1	73	15.2	19	15.0
Obstruction	52	4.8	42	8.7	12	9.5
Hypersecretion	73	6.7	42	8.7	5	3.9
Perforation	12	1.1	8	1.7	24	19.1
Hour glass contracture	7	0.6	7	1.4	4	3.1
Jejunal ulcer	0		47	9.7	0	

coming to the hospital. An almost equal number were unquestionably better, 51 per cent were improved in a minor degree, and only 13.6 per cent showed that the treatment had definitely failed. Thus 81 per cent of the patients were successfully treated—a figure which is in substantial agreement with the published results obtained in other clinics.

In analyzing the results of specific therapeutic measures it was necessary to distinguish between treatments and patients. Many patients had more than one operation, or several distinct medical schedules, and the value of each was estimated at the beginning of the next. A comparison of the medical treatments with the surgical (table 4) shows that operations gave a higher percentage of continuous relief, which should be predicted from the permanent character of some of them. But the surgical failures were more than double the medical failures, and the proportion of satisfactory results was distinctly lower.

The reasons for failure of treatment are shown in table 5. The parallelism of the medical and surgical groups is obvious. It is worthy of emphasis that in general surgical intervention was less fortunate than medical treatment in warding off pain, hemorrhage, obstruction, perforation and hour-glass contractures. Jejunal ulcers followed 11.3

per cent of gastro-enterostomies, 12 per cent of gastro-enterostomies with resection of the pylorus or a portion of the stomach, 23.1 per cent of those with excision of the ulcer and 16 per cent of those with transection of the pylorus. Seven jejunal ulcers perforated into the colon, causing gastrocolic fistulas.

This apparently unfavorable result of surgical treatment may be explained in one of two ways. Patients who were operated on had ulcers more difficult to treat or more severe. Perforation and obstruction are not treated medically. Eighty-one per cent of the surgical cases and only 60 per cent of the medical cases showed a definite complication of the ulcer. The results in such cases may be expected to be worse than in simpler cases, particularly when second and third operations are performed. That this is not the whole explanation, however, is shown by a study of table 6, which shows that in uncomplicated

TABLE 6—*Results of 426 Medical and 90 Surgical Treatments in Patients with Peptic Ulcer Without Complications\**

Results	Medical Cases		Surgical Cases	
	Number of Cases	Percentage	Number of Cases	Percentage
No symptoms	86	20.1	24	26.4
Very few symptoms	184	43.1	18	20.0
Definitely improved	112	26.3	22	24.4
Improved	15	3.5	10	11.1
Unimproved	29	6.8	16	17.7

\* A comparison with table 2 shows that the ratios are the same as for all the cases.

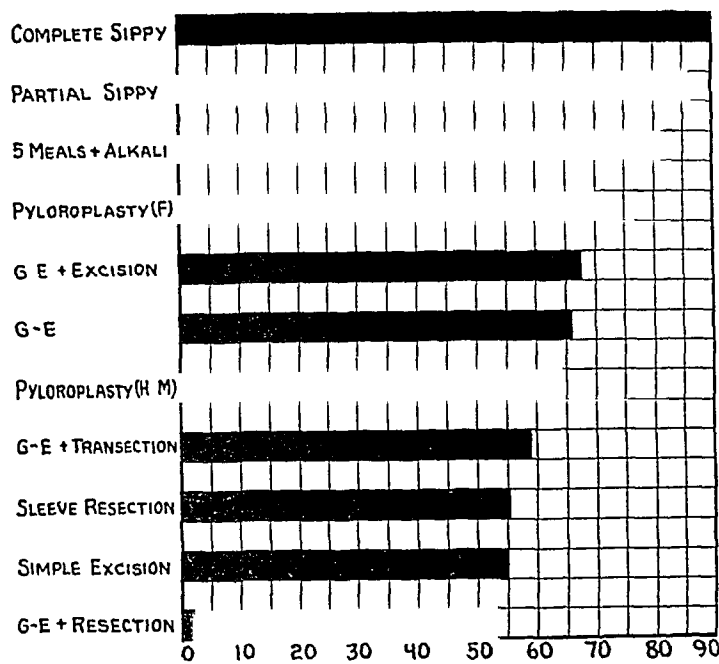
cases the proportions of good and poor results are essentially the same as for the whole group (table 4).

Surgical intervention appears to be just as unable to alter the course of peptic ulcer as medical treatment, and the true explanation for the unsatisfactory results seems to be that patients who have been operated on have not been offered or have not accepted so much attention to their general health and after-care as those treated medically. Physicians have had the feeling that surgical intervention may cure while medical measures would only relieve, and they have been inclined to tell patients after their operation to forget that they ever had an ulcer. While the physicians have been completely disillusioned on this score, the patients have not been. It is still difficult to persuade them of the necessity of after-care in the way of diet and attention to general hygiene, rest, care of infections and other measures designed to prevent relapses.

The same point is demonstrated in a survey of the results of individual types of treatment (table 7 and chart). All the medical measures gave better results than the surgical. An important reason for this is that these patients received much more attention. They had been taught the nature of their disease and were willing to report when asked and

to take good care of themselves Patients who were operated on were harder to impress as to the necessity of after-care, being prone to consider themselves cured and immune from relapses

The patients who took a complete Sippy<sup>19</sup> treatment are known to have had complete neutralization of their gastric contents for from nine



Percentage of satisfactory results obtained in 480 surgical and 1,085 medical treatments of peptic ulcer

TABLE 7—Results of 1,565 Therapeutic Measures in 1,258 Patients with Peptic Ulcer

Type of Treatment	Num ber of Cases	Per centage with No Symp toms	Per- centage with Very Few Symp toms	Per centage Defi nitely Im proved	Per centage Im proved	Per centage Unim proved
Five meals, alkaline powders	938	13.1	36.7	30.3	6.4	13.3
Partial Sippy treatment	89	13.4	38.2	33.5	6.7	7.8
Complete Sippy treatment	58	25.0	31.0	34.4	5.1	5.1
Gastro enterostomy	238	22.6	18.9	24.7	6.2	27.3
Gastro enterostomy with excision of ulcer	34	23.5	20.6	23.5	11.8	20.6
Gastro enterostomy with resection of stom ach	53	13.8	24.1	15.5	5.1	41.3
Gastro enterostomy with division of py lorus	31	16.1	12.9	29.3	3.2	38.7
Pyloroplasty (Finney)	43	20.9	23.3	25.5	11.7	18.6
Pyloroplasty (Heineke Mikulicz)	11	9.0	18.1	36.3	9.0	27.2
Simple excision	56	8.9	17.8	28.5	16.2	28.5
Sleeve resection	9	11.1	11.1	33.3	11.1	33.3

to twelve months Those who followed the treatment for from four to nine months or who failed to maintain neutralization were said to have had a partial Sippy treatment<sup>11</sup> All the others are grouped under the

19 Sippy, B W Gastric and Duodenal Ulcers Medical Cure by an Efficient Removal of Gastric Juice Corrosion, J A M A 64 1625 (May 15) 1915

heading "five meals and alkaline powders", they received a bland, non-irritating diet with one or more interpolated meals. They also received variable amounts of alkaline powders, although no attempt was made to neutralize the gastric acidity completely. This group also included patients who were started on the Sippy treatment while in the hospital but failed to keep it up after being discharged, often owing to the fact that it conflicted with their work. That the best results were obtained with the complete Sippy regimen may be due, as some believe, to a more complete healing of the ulcer, but it is our impression that the maintenance of a rigid schedule is the more important factor. This is suggested also by noting that the next best results followed a partial Sippy treatment and that the poorest results followed the rather lax "five meal and alkaline powder" program. The outcome seemed to vary according to the willingness of the patient to follow directions in detail as to his habits of living. Many of the patients in the "five meal" group really achieved more neutralization than some of those who took a partial Sippy treatment but were led to believe in a false security because of freedom from symptoms and paid less attention to general hygiene and rest.

None of the operative procedures attained as high a degree of satisfactory results. A simple posterior gastro-entrostomy, sometimes with plication of the pylorus, was the commonest operation, and it proved almost as effective as when excision of the ulcer was added to it. Pyloroplasty in some form was in the same rank. Distinctly less favorable results followed operations in which the surgeon thought it necessary to add a division (transection) of the pylorus or removal of the pylorus or some portion of the stomach. In these cases the patients also proved most refractory to subsequent medical treatment. Removal of the antrum was proposed with the idea that the loss of its hormone would decrease the production of hydrochloric acid. Experience has shown this to be a mistake. Since the operation removes the part of the stomach which has an alkaline secretion it should be abandoned.

Other types of operation gave equally poor results, but they were often performed on patients who were in bad condition, had adhesions or had suffered acute perforation, so that no other course was open. The figures are not a criticism of the procedure but simply an illustration of the difficulties of the situation. We are getting better surgical results since the choice of operative procedure has been guided by a knowledge of the possible results and since the postoperative care is applied early and is kept up. We have long since rid ourselves of the notion that one form of therapy is far superior to all others. We recognize that success depends on an acquaintance with all forms and on the ability to use whichever fits the individual case.

Table 8 shows that the longer one follows patients with peptic ulcer the fewer are his medical "cures." Surgical "cures" maintain themselves at a consistently higher level after the first year. Medical failures also tend to become fewer as time goes on, and so do those following surgical procedures. In other words, more and more cases fall into or are lifted up to the ranks of the satisfactorily improved.

#### TREATMENT OF ULCER AS A CHRONIC DISEASE

*Treatment of Uncomplicated Peptic Ulcer*—Two convictions were brought home to us early in our experience with cases of peptic ulcer. One was that the disease is primarily a problem for the physician, and the other, that the strict Sippy regimen was the best medical solution. Time has clarified these views. Surgical intervention is at times indispensable, even life-saving, but it does not cure the disease or alter its

TABLE 8—*Influence of the Duration of Observation on the Number of Cures and Failures in the Treatment of Peptic Ulcer*

Period of Observation in Years	Number of Patients Cured		Number of Patients Unimproved	
	Percentage with Medical Treatment	Percentage with Surgical Treatment	Percentage with Medical Treatment	Percentage with Surgical Treatment
0-1	21.4	7.9	17.4	39.4
1-2	16.3	23.3	6.0	23.3
2-3	15.3	38.8	9.2	24.0
3-4	16.6	15.6	9.5	19.5
4-5	13.8	14.8	2.7	25.9
5-6	7.4	19.0	9.2	19.0
6-10	8.4	22.9	4.6	5.4
11-15	7.4	18.5	14.0	11.1

tendency to persist. Since it carries a mortality which equals or exceeds the chance of the patient with ulcer to die of the disease at the age of 59, it should be used sparingly and only for very definite indications. How, then, shall one go about the treatment in a case of duodenal ulcer and no complication—the average case?

In the first place, the importance of a thorough study of the case is to be emphasized. A complete physical examination is required, as well as routine analyses of the blood, urine and stool, a Wassermann test and a gastric analysis. One must acquaint himself with the past history of the patient, with the details of the status of the systems other than the gastro-intestinal tract and with the social and economic situation. Obviously, certain diseases, such as cholecystitis and intestinal disturbances, may have an important influence on the symptomatology of the peptic ulcer and may compel alterations in its treatment. Other diseases, such as carious teeth and recurrent infections of the tonsils, may affect the ulcer by disturbing the general state of health. It is impossible to

treat the ulcer alone. When a physician accepts the responsibility for such a case he must be prepared to treat, or superintend the treatment of, the whole person. He must be alert to the need for repeated physical and laboratory examinations, lest he overlook complications or intercurrent disease—errors lying in the path of all who deal with chronic disease.

We have found it wise to tell the patient frankly the nature of his disease. We tell him that the ulcer does not seriously threaten his life and does not tend to progress in severity, although it may interfere with his comfort and his activity from time to time. We confess that there is no known means of effecting a permanent cure but reassure him that there are various conservative measures which are able to make him comfortable and efficient at work, and we advise him as to the necessity of henceforth reporting regularly to his doctor. We have pursued this policy for the last six years, both with patients at the clinic and with private patients, and we have been greatly impressed with its value. It generates a spirit of cordial and intelligent cooperation. Most patients are secretly convinced of the chronicity of their trouble before the physician sees them. When their fears are confirmed and allayed they are transformed from a restless, dissatisfied group wandering from doctor to doctor into one that realizes the need for daily care, for attention to hygiene and for occasional medical investigation.

It is necessary to discover any causes that may account for the activity of the disease in each particular patient. If he is of a worrisome disposition or unstable emotionally he must be shown the importance of leading an even-tempered existence for the sake of his ulcer. One man, a dentist, not included in this series, has found that he pays for an outburst of anger by a few days of ulcer pain, and he has achieved a comfortable existence by becoming phlegmatic. Even if the patient is a perfectly calm person he will learn the wisdom of resorting to treatment for his ulcer during mental or economic crises. We are impressed by the number of patients with intractable pain and by the number of those that require prolonged, meticulous attention to treatment who by nature or by force of circumstances are exposed to much nervous wear and tear. Others are not bothered by such factors but have trouble during periods of physical fatigue. Still others find that minor infections of the respiratory tract are their only consistent enemy. It is the task of the physician to study these individual characteristics and to include their elimination in his treatment.

Rest is absolutely essential in the treatment of every patient with ulcer, but the problem of how much rest is needed cannot be settled in general terms for all the cases. Sippy advised hospitalization for a month, others still insist on this or its equivalent in any other neutral environment. Although this is essential in some of the more severe



cases it is not necessary for many patients, to some of whom it is a great economic hardship. Some patients do well with a few more hours in bed each day than they have been accustomed to allot themselves. At first they may require twelve hours each night, and a midday nap, later they may find nine hours sufficient. It is our experience that less than eight hours of rest each day is suboptimal and may result in the accumulation of enough fatigue to precipitate an attack of ulcer pain or to prevent healing in the active stage. Mild hypnotics may be useful for short periods to counteract insomnia due to nervous fatigue. The individual patient must determine, with the supervision of his physician, how much and what sort of rest and relaxation he requires, not only during the stage of symptoms but for the free intervals as well. The variety of patients' occupation and pursuits at times calls for the exercise of much ingenuity.

The diet must meet several requirements. 1 It must have balance, there must be no lack of necessary minerals, vitamins and food substances. Too rigid restrictions are unwise when the treatment must be so prolonged, and there are reports in the medical literature of deficiency diseases occurring as a result of such restrictions. 2 It should consist of foods which are not too coarse. This means that meats must be chopped finely and vegetables must be strained. Ivy<sup>20</sup> has shown that a diet of bland foods allows an artificial ulcer to heal more rapidly than a diet of coarse foods. A few patients can be trusted to masticate food so thoroughly that the preparation of their food need not be different from that of other members of their family. For most patients it is wiser to insist that their food must permanently receive these attentions. 3 Finally, condiments should be used sparingly, although a minimum necessary for palatability may be allowed. Alcohol in any form and carbonated drinks seem definitely contraindicated. We are rather lenient as to tobacco. Some of our patients smoke without any apparent harm, and they need not be denied this solace in moderation. Others find by trial that irritation of the ulcer is caused by smoking, and they should become abstainers.

Alkalis are useful for the relief of pain in the early stages but do not aid healing unless complete neutralization is accomplished. However, their use should be discouraged so far as possible in order to prevent the patient's relying on them to the neglect of other measures which do promote healing. They can be satisfactorily given according to Sippy's formula (calcium carbonate, 0.6 Gm., sodium bicarbonate, 2 Gm.) They may be given in individual powders, in bulk or in tablet form. When

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20 Ivy, A. C., and Fauley, G. B. Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine. II. Effect of Diet on Healing of Acute Gastric Ulcer. *Am. J. Surg.* **11**: 531 (March) 1931.

constipation requires attention magnesium oxide as suggested by Sippy is useful. These powders have proved to be so satisfactory that we have not found it necessary to use other alkalis, such as precipitated calcium phosphate.

Belladonna in some form is occasionally valuable for patients who have intestinal distress. It does not seem to affect the ulcer distress. Our experience with mucin has not been satisfactory, and we have discarded it because it is unpleasant to take.

The diet and the schedule advocated by Sippy meet all the requirements. By the use of this treatment it is possible to control completely the corrosive action of the gastric juice, which no modification can do. The difficulty of its application would be no argument against it if it could effect permanent cures. Our experience has been, however, that patients tend to relapse as frequently after the Sippy treatment as after any other if they are permitted to return to their former mode of living. Moreover, as Nicholas and Moncrieff<sup>17</sup> have pointed out, ulcers heal in the presence of hydrochloric acid, so that complete prolonged neutralization is not necessary. In most of our uncomplicated cases, therefore, we have abandoned the Sippy regimen, particularly for patients who find it an economic hardship, cannot leave their work or cannot continue it after returning to work.

A "modified Sippy regimen" is of course no different from any other plan which relies on frequent feedings and doses of alkaline powders. Symptoms of ulcer disappear quickly following any of them, but if the general situation is not controlled an active, open ulcer may persist and make itself known just as quickly when the treatment is stopped. The powders may be used for only a few weeks or months, dietary restrictions may be eased later on, but rest from physical and nervous fatigue, avoidance of infection and care of other factors must be insisted on if the treatment is to be made really adequate.

What is to be done if this treatment fails to "cure"? Such a lack of perfection is to be expected from the nature of the disease, but this does not mean that very good results are not possible. A patient with peptic ulcer has an active or potentially active lesion for the rest of his life, so far as we can tell. Treatment does not stop with the clearance of symptoms or a short time after, as it used to. The general hygienic measures are continuous, the use of alkaline powders and strict diet schedules may be repeated as often as necessary and are always effective in uncomplicated cases. One should not lose faith in the treatment because of relapses, and resort impatiently to more radical measures. In some cases complications will develop—there is no sure way of telling in which ones this will occur. The complications will be treated sooner if the possibility of their occurring is always borne in mind than if a remission is regarded as a cure. It is our conviction that the number

of complications has decreased since we have established permanent supervision

Uncomplicated gastric ulcers are to be treated in the same way, although they require closer supervision. It has been our experience<sup>1</sup> that such ulcers are or become malignant in only about 5 per cent of the cases. Because the experience at the Mayo Clinic<sup>21</sup> has been quite different, because there is no way of telling offhand whether any particular case is benign and because of Holmes'<sup>22</sup> recent emphasis on the dangers of lesions about the antrum we established the following plan, which has worked satisfactorily. A patient whose roentgenograms show a gastric ulcer is required to stay in the hospital for three weeks on a strict Sippy schedule, and the roentgenographic study of the stomach is repeated. If this shows no healing as compared to the first examination immediate operation is advised. If the healing is definite, the ulcer crater being smaller, medical treatment is continued. Roentgen studies are made again three months and six months later and then at least once a year, to make sure that this confidence is justified.

*Treatment of Peptic Ulcer Causing Obstruction*—It is important to distinguish between retention and obstruction. With the present reliance on the roentgenologist for diagnosis there has been a strong tendency for the physician to assume that the two terms are synonymous. Fluoroscopic evidence that radiopaque material has remained in the stomach for six hours does not tell why it has done so. Obstruction is the retention of material in the stomach for an abnormal period of time owing to cicatricial narrowing about the ulcer. However, retention may be due to other causes, such as apprehension over the examination, headache or nausea, local swelling and edema about an ulcer or pylorospasm. A distinction between these temporary and permanent factors can be made by the repetition of the roentgen study after a short test of medical treatment and by a comparison with the clinical findings, such as a history of vomiting of food for some time with a loss of weight and the demonstration of food residues in the fasting stomach.

These facts, which are well known to roentgenologists and students of the disease, were pointed out by us in an earlier paper<sup>15</sup>. It was also suggested there that barium sulphate is an abnormal material for the stomach to deal with and that what the physician who treats the patient needs to know is how ordinary food fares in the stomach. In some cases the heavy salt pours through the pylorus so rapidly as to cause a

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21 Alvarez, W. C. *Diseases of the Stomach*, in Christian, Henry A. Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1931.

22 Holmes, G. W., and Hampton, A. O. Importance of Location in Differential Diagnosis of Benign and Malignant Gastric Ulcerations, *New England J Med* 208:971 (May 11) 1933.

real obstruction to be missed, in a few other cases it settles in the region of the stomach below the obstruction, and overemphasizes the true state of affairs. Therefore, surgical measures need not be advised indiscriminately for all cases of retention.

Statistics on our present series of cases show that obstruction of some degree was found in 169 cases (11.7 per cent). Of 266 cases in which a comparison of the roentgen and clinical evidence of retention could be made, there was agreement in 141 (53 per cent). This was most common in the cases in which a large residue was shown by fluoroscopic examination (71 per cent of the cases showing from 30 to 60 per cent retention, and 91 per cent of those showing from 60 to 100 per cent retention at six hours). Disagreement between the results obtained by the two methods occurred almost entirely in the cases in which small residues were observed under fluoroscopic examination (29 per cent). The 9 per cent showing a large roentgen retention but no clinical obstruction were the cases of reflex spasm due to headache, nervousness, etc.

Medical treatment was much less satisfactory in the cases showing clinical confirmation of the roentgen evidence of obstruction than in the others. Medical treatment was effective in only 38.6 per cent of the cases in which the gastric aspirations and the history agreed with the roentgen findings. It helped in 68.2 per cent of the cases in which the roentgenogram alone suggested retention. Surgical treatment was much more efficacious in patients with high grade obstruction than in those with less than 40 per cent retention. Below this level medical and surgical measures were equally effective.

It seems wise, therefore, in every case to test the roentgen evidence of obstruction with the clinical evidence and with a short trial of careful medical treatment. If the two disagree and the six hour retention is small such a treatment is apt to be sufficient, for it is unlikely that an important degree of permanent blockage is present. If the two agree and the large residue persists on a second roentgen examination it is useless to delay operation any longer.

*Treatment of Peptic Ulcer with Hemorrhage*—Hemorrhage is a dramatic complication of peptic ulcer, terrifying to the patient and his friends and by its threat of a calamitous outcome often impelling the physician to use extravagant therapy. A knowledge of what the average hemorrhage means to the average patient with ulcers proves of great comfort to all the parties concerned, and suggests a reasonable plan of treatment.

In our previously reported series<sup>1</sup> the incidence of hemorrhage was 34.8 per cent, a figure which was in agreement with most early statistics. Now, with the number of cases nearly trebled, we find only 38.4 patients, or 26.7 per cent, who have bled at some time. This decrease is probably

due to the recognition of many milder cases rather than to any improvement in our method of treatment, for other recent writers have noted an even lesser incidence. It is perhaps fair to state that 1 of every 4 patients with ulcer will suffer from a hemorrhage at some time in his life.

There is no way of telling which patients will bleed. Some do so at the apparent onset of the disease, others at later periods even up to fifty years after the onset. Some seem to have a persistent hemorrhagic tendency, and others "outgrow" it or acquire it. Up to 1932, 20 of our patients, that is 5.2 per cent of those who have bled or 1.3 per cent of the total number, died of hemorrhage. Thus a hemorrhage from a peptic ulcer carries only a small threat to life. Its economic importance is greater, for it forces the patient to leave his work and incur expenses of hospital and professional attendance for weeks.

Hemorrhage presents two problems in therapy: how to deal with the acute stage and how to prevent a future loss of blood. Surgeons naturally prefer not to operate on an already anemic patient who is actively bleeding. But whenever one is called on to treat a patient who continues to bleed despite medical management there is a great urge to call for the help of surgical measures. As the incidence of death is less than the mortality associated with gastric operations it seems better to follow the rule that hemorrhage from ulcer is a medical problem entirely. In 95 per cent of the cases the bleeding stops spontaneously, and it is the job of the physician to prevent its recurrence. At present there is no way of saving the 5 per cent who continue to bleed until death supervenes, for it is only in this relatively small group that surgical intervention is justified, and unfortunately there is no way of telling which patients are going to fall in this group.

The belief is prevalent that patients are less likely to bleed after surgical than after medical treatment, and there is a tendency to advocate surgical intervention whenever a patient has had some severe bleeding. Our figures do not lend any justification to this belief. The relation of treatment to the incidence of hemorrhage has been recorded for 380 patients (table 9). Of 202 patients, 19.3 per cent have bled after medical treatment during an average period of observation of three and six-tenths years. Of 155 patients who received surgical treatment, 17.4 per cent had another hemorrhage within an average period of four and eight-tenths years. Even if we make a correction for the difference in the time of observation and allow for a greater tendency to bleed in the surgical cases it is still clear that surgical intervention does not prevent future hemorrhages any more than does medical treatment. Table 9 illustrates this fact in detail.

A single hemorrhage is therefore not an indication for surgical intervention. In spite of this fact clinical experience shows that a certain

number of patients who bleed frequently on medical treatment cease to bleed after operation. Therefore, when it becomes established that patients have a hemorrhagic tendency recourse should be had to surgical procedures. For the immediate treatment of the bleeding patient, we have had the best results with the plan established by Sippy.

TABLE 9—*Occurrence of Hemorrhage in Relation to the Treatment*

Type of Treatment	Number of Patients Treated	Percentage with Hemorrhage Before Treatment Only	Percentage with Hemorrhage After Treatment Only	Percentage with Hemorrhage Both Before and After Treatment
Medical	202	64.5	15.8	19.3
Surgical	155	61.9	20.6	17.4
No treatment	23	48.0	26.0	26.0

\* The groups are similar, but there is a greater tendency for hemorrhage to occur after surgical than after medical treatment.

TABLE 10—*Frequency with Which Complications Occurred in Relation to Various Amounts of Free Hydrochloric Acid in the Gastric Contents of 994 Patients with Peptic Ulcer \**

Free Hydrochloric Acid	Number of Patients	Percentage with No Complications	Percentage with Obstruction	Percentage with Hemorrhage	Percentage with Perforation	Percentage with Hour Glass Contracture	Percentage with Jejunal Ulcer
0-20	128	53.9	13.2	22.6	3.9	1.5	4.6
21-40	224	46.9	22.3	22.3	3.1	2.2	3.1
41-60	290	47.2	20.6	22.4	3.1	2.7	3.7
61-80	214	47.6	18.7	25.7	3.2	0.4	4.2
81 plus	138	46.3	19.5	24.6	5.0		4.3

\* No analyses were done on other patients. The highest level of free acid was taken in each case. The complications are strikingly similar at each level.

TABLE 11—*Percentage of Satisfactory Results of Treatment in Relation to Different Grades of Acidity \**

Free Hydrochloric Acid	Number of Patients Showing Satisfactory Results	Percentage
0-20	73	63.4
21-40	135	66.1
41-60	191	72.6
61-80	130	63.7
81 plus	67	57.2

\* The figures represent the highest amount of free hydrochloric acid in the 888 patients that were followed.

*Treatment of Peptic Ulcer with Hyperacidity*—A small group of patients with ulcers respond poorly to all routine treatment. They are not long without pain on medical measures, pain at night is very common. They are usually of a very nervous temperament, and their gastric contents have high degrees of free acidity. Attempts to overcome this condition by increasing the administration of the alkaline powders results

in a still greater secretion of acid and in the appearance of toxic symptoms (alkalosis). In most instances surgical measures are followed quickly by the formation of jejunal ulcers, which are still more intractable. We therefore came to regard hyperacidity as a definite complication of peptic ulcer.

An analysis of our cases shows that this belief was wrong and that hyperacidity alone is not a complication. Table 10 shows the values for acid in the gastric contents of the 994 patients on whom analyses were made. Since the incidence of complications is the same whatever the level of free acid and since the acidity seems not to influence the results of treatment (table 11), whether medical or surgical, the severity of the ulcer cannot be judged by the height of the curve for acid. The difficulty lies rather in the amount of acid secreted. The stomach forms acid at a fixed concentration, and the figures from titration depend on the amount of neutralization which has taken place. High degrees of acidity may result from inadequate neutralization or from the production of greater quantities of acid than the normal processes can cope with. It is in patients with hypersecretion that difficulties of treatment are encountered.

The presence of hypersecretion may be suspected by the presence of the following conditions:<sup>23</sup> (1) the persistence of pain at night after the patient should be relieved by treatment, (2) an inability to neutralize the gastric acidity completely by means of the Sippy regimen, and (3) a tendency for the stomach to produce a greater quantity of acid as the amount of alkali is increased. Proof is forthcoming if a secretion persists in a fasting stomach. This is best determined, as suggested by Henning and Norpath,<sup>24</sup> by allowing a nasal tube to remain in the stomach during the night and performing frequent aspirations.

The presence of hypersecretion requires extreme caution in treatment. The patient must be confined to bed in a hospital for several weeks and be given frequent feedings of a very bland diet and milk and cream every hour. Alkaline powders are contraindicated. Sedatives are usually necessary to control nervousness and to secure restful sleep. After the symptoms are fully allayed the diet is gradually increased and the number of doses of milk and cream decreased until the schedule is that used in the uncomplicated case. Subsequent care and attention to general hygienic measures are also important. Since jejunal ulcers are prone to develop in these patients surgical procedures must be

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23 Emery, E. S., Jr. The Treatment of Peptic Ulcer Complicated by Hypersecretion, *New England J. Med.* **210** 637 (March 22) 1934.

24 Henning, H., and Norpath, L. Investigations on Secretory Function of Stomach During Night Sleep, *Arch. f. Verdauungskr.* **53** 64 (Jan.) 1933.

avoided. Roentgen therapy is sometimes useful as a palliative measure in these cases in order to bring the condition under control <sup>25</sup>

*Treatment of Ulcer with Perforation*—It is generally recognized that acute perforation must be repaired surgically as soon as possible and that disasters increase rapidly as treatment is delayed. Difficulty in diagnosis was the usual cause of delay in our experience, many of our patients having entered the hospital from twelve to forty-eight hours after the onset. Ten patients had a chronic perforation which was recognized for the first time at the operating table or at necropsy. It seems that the only way to improve this situation is to consider every peptic ulcer as a potentially perforating ulcer for the remainder of the patient's life. While the incidence is small (111 cases, or 7.7 per cent), we know of no way of predicting in which cases perforation will occur. Certainly it has been demonstrated amply that roentgenologic reports of "perforating types" of ulcers are misleading, since they are no more likely to rupture than any other type. If the possibility is kept in mind, an acute abdominal upset in a patient with an ulcer may be distinguished as perforation at the earliest possible moment.

Simple closure of the perforation with or without gastro-enterostomy has proved effective, and the patients prove no more difficult to treat later than other patients with ulcers. In our series 18 (16.2 per cent) had no symptoms afterward, and satisfactory results were obtained in 66 (59.4 per cent). Thirty-five patients (31.5 per cent) were unimproved, 32 of these died, most of them being moribund before treatment could be instituted. Those who were in good condition were not harder to take care of than other patients who have been operated on. Seven jejunal ulcers perforated into the colon, causing a gastrocolic fistula and a very difficult technical situation for the surgeon.

#### SUMMARY

This study of a large group of patients with chronic peptic ulcer of the stomach or duodenum over a long period of years shows that the disease tends to persist throughout life when once it is established. It is caused by some factor or factors which are not yet known. More appears to be involved than the local lesion in the mucous membrane, which heals spontaneously or under treatment and then breaks down again. The disease is rarely fatal and does not generally shorten life. Although it is subject to certain complications, in the average case it does not tend to get worse as time goes on.

It is demonstrated that none of the present methods of treatment do more than assist in the induction of remissions, no matter how strict

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<sup>25</sup> Emery, E. S., Jr. Peptic Ulcer. Its Treatment by Roentgen-Ray, New England J. Med. **206** 717 (April 7) 1932.



the medical schedule or how radical the operation. Surgical procedures produce longer periods of freedom from symptoms than medical treatment, but the former also carry a definite threat to life and often produce mechanical situations which make subsequent attacks difficult to control. A plan of conservative treatment is offered which seeks to produce the best possible results with the least cost to the patient. Its most important aspect is that it seeks to govern the patient's total situation, trying to prevent or minimize factors which may cause a relapse. The most important offenders known are fatigue, worry and infection. Surgical intervention is resorted to for definite purposes, namely, to close a perforation, to overcome a permanent obstruction of more than 40 per cent as seen by fluoroscopic examination six hours after a meal of barium and to attempt to overcome a hemorrhagic tendency, it is also resorted to in cases in which there is a reasonable suspicion of cancer or malignant degeneration. The operation of choice is that which accomplishes the specific purpose in view and interferes as little as possible with the physiologic action of the stomach. Subsequently the patient is to be treated as all other patients with ulcer who have not been operated on. During periods of hypersecretion the patient is to be treated with particular care medically, operation at such a time is disastrous.

# TRANSVERSE DIAMETER OF THE HEART IN PATIENTS WITH HYPERTENSION

WITH CLINICAL MEASUREMENTS CHECKED BY POSTMORTEM STUDIES

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Since the advent of the use of roentgen rays in the diagnosis of cardiac disturbance, accurate measurement of the size of the heart has become a routine procedure. In the attempt to distinguish between the normal and the abnormal cardiac silhouette various measurements have been suggested,<sup>1</sup> of which the transverse diameter, because of the ease and accuracy of determination, has received the widest favor. However, it was found that average or arbitrarily set limits of the normal width were not reliable as a guide to cardiac enlargement in the individual instance. In 1919, Danzer<sup>2</sup> proposed the ratio of the transverse diameter of the heart to the internal diameter of the chest, determined on a roentgen-ray shadow on a film taken 6 feet (1.8 meters) from the tube, as a criterion of the normal size of the heart. He believed that there is a constancy of relationship between the two measurements, such that the ratio of 1:2 is not exceeded in normal persons despite variations in the body habitus. The data on which this assumption was based were not given. He admitted, however, that in thin-chested, asthenic persons cardiac hypertrophy and/or dilatation might be present, but were not evident by this method of measurement.

In 1926, Hodges and Eyster<sup>3</sup> attempted to define by statistical methods the normal transverse cardiac diameter as correlated with age, sex, height and weight. The width of the heart was determined on 80 persons by means of the orthodiagram, which obviates the exaggeration of the cardiac shadow and width of the chest inherent in the method of teleoroentgenography. Statistical analysis showed that nor-

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1 Eyster, J. A. E. Determination of Cardiac Hypertrophy by Roentgen-Ray Methods, *Arch Int Med* **41** 667 (May) 1928

2 Danzer, S. D. The Cardiothoracic Ratio. An Index of Cardiac Enlargement, *Am J M Sc* **157** 513 (April) 1919

3 Hodges, F. J., and Eyster, J. A. E. Estimation of Transverse Cardiac Diameter in Man, *Arch Int Med* **37** 707 (May) 1926

mally a correlation exists between the factors mentioned and the transverse cardiac diameter, most evident in the case of body weight. A formula was devised for predicting the normal width of the heart as disclosed by the orthodiagram in the individual instance. It was of such statistical accuracy that if the actual measurement exceeded the one predicted by as little as 5 mm the chances were three to one that the enlargement was abnormal. However, they stated that this formula was only 19 per cent more accurate than an assumed average normal for all cases and little better than random guessing.

In a further study,<sup>1</sup> dealing with attempts to determine a closer degree of correlation between the size of the heart and bodily measurements, Eyster compared this standard with the Danzer ratio in 100 normal persons and in a similar number of persons with various types of heart disease. He found that by the cardiothoracic ratio 94 per cent of the group of normal persons had a transverse cardiac diameter less than one half the internal diameter of the chest, but that this was also true in 38 per cent of those with a pathologic condition. Only 42 per cent of the latter series had a ratio definitely indicative of cardiac enlargement. The prediction figures gave distinctly better results. Only 8 of 100 normal persons had actual transverse diameters above 10 per cent of the predicted normal, whereas 78 per cent of those with a pathologic condition had actual transverse diameters exceeding this figure. Banton,<sup>4</sup> comparing these standards in 97 males and 75 females who had no evidence of heart disease, obtained a similar discrepancy, which will be dealt with in detail later. In a recent study,<sup>5</sup> the same observer applied the prediction figures of Hodges and Eyster to 470 patients, of whom 44 had functional cardiac disturbance, 70, a questionable diagnosis of cardiac involvement, and 357, organic heart disease. Seventy per cent of the latter had transverse cardiac diameters exceeding by more than 0.5 cm the predicted normal. One hundred and thirty of the 357 in the pathologic series had hypertension, of whom 90 (69.2 per cent) had a similar degree of cardiac enlargement. He did not utilize the Danzer ratio in this study but, on the basis of his experience with "noncardiac" subjects, concluded that it is of little value in detecting cardiac enlargement, whereas he regarded the prediction figures of Hodges and Eyster as the most efficient standard in predicting the transverse diameter of the normal heart.

To our knowledge, the efficacy of these two standards in determining cardiac enlargement has been studied in only one series of pathologic cases. It was considered worth while to recheck the results in a series

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<sup>4</sup> Banton, J. H. The Transverse Diameter of the Heart, *Am Heart J* 7: 331 (Feb) 1932.

<sup>5</sup> Banton, J. H. The Silhouette of the Heart and the Aortic Arch. Orthographic Measurements, *Am Heart J* 8: 616 (June) 1933.

of patients having potentially a uniform type of cardiac lesion, namely, hypertrophy of the left ventricle resulting from arterial hypertension. The attempt has further been made to elucidate the extraneous factors influencing the discrepancy in results obtained by the two standards and to test for the first time the validity of the conclusions offered in a small series of cases in which the actual heart weights were obtained at necropsy. The correlation with axis deviation in the electrocardiogram was also studied. Data obtained from Bainton's figures on persons without cardiac involvement have been utilized as a control series for comparison. The fact that the latter determinations were not made by us is considered desirable rather than otherwise, as the comparative results, embodying a possible multiplicity of subjective and objective error, should be applicable to the determinations made in any laboratory.

#### MATERIAL AND TECHNIC

Our series consisted of 79 patients, 50 of whom were women, with an average age of 56.6 years (youngest, 25 years, oldest, 79). The 29 men had an average age of 59 years (youngest, 22 years, oldest, 74). No attempt at selection was made beyond the assurance that each patient had a sustained systolic pressure of 150 mm. of mercury or more, and that congestive heart failure was not present as it might introduce the complicating factor of ascites, with upward displacement of the diaphragm, hydropericardium, etc.

The orthodiagram was made with the patient in the standing position, breathing quietly. The fluoroscope used has a side arm which moves synchronously with both the tube and the screen in a vertical and in a horizontal plane. The cardiac silhouette was recorded by means of pencil dots on paper, corresponding in relative position with the black dot placed at the border of the heart and marking the point of emergence of the central rays from the tube. The tracings were made by three observers, and it was found that their determinations on the same patient varied as much as 0.5 cm. in the transverse cardiac measurement. This may be regarded as a fair estimate of the experimental error. No heart was considered enlarged unless its transverse diameter exceeded by 0.5 cm. the normal measurement as given by the standard under consideration.

#### RESULTS

*In Persons Without Heart Disease*—Bainton found that in such persons the cardiothoracic index gave more of a "scatter," that is, placed more of these persons in a group with abnormally small or abnormally large hearts, than did the prediction figures of Hodges and Eyster. In table 1 the distribution by these two methods for patients without heart disease, as calculated from Bainton's data, and for our series of patients with potential cardiac enlargement, is indicated. The naught at the top indicates absolute coincidence of the predicted widths with the actual widths. The figures to the left indicate in centimeters the difference between the predicted and the actual transverse diameters of hearts smaller than normal by the two methods, and those to the right,

the difference in centimeters between the predicted and the actual transverse diameter of hearts larger than the predicted normal. It can be seen that by the method of Hodges and Eyster 41 (23.4 per cent  $\pm$  7.8) of 175 persons without heart disease had heart widths less by 1 cm, or more, than the predicted normal, that 106 (60.5 per cent  $\pm$  4.7) had cardiac widths within 0.5 cm of the predicted normal, and that in the remaining 28 (16 per cent  $\pm$  7) the results fell in the group of abnormal cardiac enlargement. However, none of the subjects had an actual transverse diameter exceeding by 2 cm the predicted normal width. Quite different results are secured by the cardiothoracic ratio, according to the figures obtained from Bainton's data. By that method 71 (41.9 per cent  $\pm$  5.9) of his 170 patients had abnormally small hearts,

TABLE 1—*Distribution of Size of Heart in Persons with and Without Potential Cardiac Enlargement*

		Minus Cm										Plus Cm											
		3.5	3.0	2.5	2.0	1.5	1.0	0.5	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0				
Prediction Figures of Hodges and Lyster	←	2   13   26   46   9   51   21   6   1																				175 normal persons	
		23 4%										60 5%										16%	
		87%																					
		Hyper tension 79 pa tients																					
		4   4   8   8   18   11   10   4   1   4   3   2   2																				69 6%	
		5%										25 3%											
		53 1%																					
		1   3   10   8   19   30   28   4   23   22   13   5   4																				Normal (170)	
		41 9%										32 3%										25 8%	
		62 9%																					
Hyper tension	{	1   1   4   5   8   3   16   17   10   5   4   1   1   3																				Cardiothoracic Index →	
		7 6%										20 2%										72 1%	
		45 5%																					

55 (32.3 per cent  $\pm$  6.2) had heart widths within normal limits, and 44 (25.8 per cent  $\pm$  6.6) had cardiac widths exceeding by at least 1 cm the predicted normal, of whom 5 had an enlargement of 2 cm and 4 of 2.5 cm. The differences in distribution obtained by the two methods in persons without heart disease are statistically suggestive and, as Bainton showed, are not influenced by sex. Bainton did not attempt to unravel the factor or factors influencing the wide distribution obtained by the Danzer ratio, but concluded that the standard was of little value as a criterion of the normal size of a heart.

*In Patients with Hypertension*—It would seem that the two standards when applied to persons with hypertrophied hearts, should show the same differences in results obtaining in persons with normal hearts, that is the prediction figures of Hodges and Eyster should give a

smaller scatter and a larger per cent of patients with abnormally great transverse cardiac diameters than would the cardiothoracic ratio. This of course postulates that the two series of patients are comparable in other respects—that there are no complicating extraneous factors. Table 1 shows that while in the series of patients with hypertension the magnitude of the scatter obtained by the two standards is of relatively the same degree as that present in the group with no cardiac involvement, the percentage of enlarged hearts (prediction figures of Hodges and Eyster, 69.6 per cent  $\pm$  6.1, Danzer ratio, 72.1 per cent  $\pm$  6) is approximately the same by both standards. The two methods show a surprising degree of correlation throughout. Hodges and Eyster's standard gave no enlargement in 24 (25.3 per cent  $\pm$  8.8) of 79 patients and the Danzer ratio, no enlargement in 22 (20.2 per cent  $\pm$  8.5). There was no enlargement by either method in 17 (21.5 per cent  $\pm$  9.6) of the patients. It is evident that there must be a factor, or factors, influencing the cardiothoracic ratio in our series of patients which was not operative in Banton's series, for, if it were to be imagined that in his 71 patients with abnormally small hearts there developed a cardiac enlargement of 1 or 2 cm, this would place them in the group of persons with hearts of normal size instead of in the group with cardiac enlargement, while the Hodges and Eyster standard would presumably shift them well to the right in the diagram, thus maintaining the discrepancy in results obtained by the two standards.

In attempting to elucidate the factor, or factors, at work in our series, we first studied those cases in which the results obtained by the two standards were in disagreement as to the presence of cardiac enlargement. This occurred in 17 (20.5 per cent) of the 79 cases, exceeding the experimental error of the determination in 13 (16.4 per cent  $\pm$  3.2). The pertinent data in each instance are recorded in table 2. Of the 7 patients with significant cardiac enlargement by the Danzer ratio only, 6 were women. With one possible exception (case 18), all of the subjects were obese. Conversely, a tendency to underweight is apparent in the series of 5 patients having a significant cardiac enlargement by the Hodges and Eyster standard alone. This suggested a comparison of the two standards in the underweight and overweight persons in our series. To avoid the complicating factor of sex, women only were selected. The results are given in table 3, and for the sake of completeness the remaining cases in our series are listed in table 4. There were 17 women classifiable as obese. All but 1 had cardiac enlargement by the Danzer ratio, averaging for the group 1.8 cm  $\pm$  0.03. Five had hearts of normal width, or less, as judged by the Hodges and Eyster standard, giving an average enlargement for the group of 0.7 cm  $\pm$  0.02, the difference by the two methods averaging 1.1 cm  $\pm$  0.1. In 9 underweight women a converse tendency was obvious: the prediction figures

TABLE 2—*Enlargement of the Heart*

By Danzer Ratio Only												
Case	Age	Sex	Height		Weight, Lb	Average Blood Pressure	Known Duration	One Half	Actual	Enlarge	Predicted	Enlarge
			Ft	In				Chest Diam eter, Cm	Trans verse Cardiac Diameter, Cm		ment, Cm	
18	80	F	5	0	135	165/120	?	10 0	11 3	1 3	11 6	
31	71	M	5	11	184	170/ 80	2 to 3 yr	11 2	13 5	2 3	13 6	
32	58	F	5	2	220	150/ 85	?	12 0	12 9	0 9	14 3	
60	64	F	5	2	174	210/120	?	10 7	12 2	1 5	12 7	
69	73	M	6	6	173	155/ 80	?	12 0	12 2	0 2	12 9	
93	50	F	5	7	150	150/100	12 yr	11 3	11 5	0 2	11 5	
12	59	F	5	6	174	180/110	10 yr	9 9	12 0	2 1	12 5	
29	52	F	5	5	165	180/ 90	?	11 0	11 9	0 9	12 2	
40	61	F	5	5	213	210/110	?	12 0	13 5	1 5	14 1	
73	67	M	5	10	176	185/110	7 mo	12 0	13 1	1 1	13 2	
By Prediction Figures Only												
85	44	M	5	10	169	180/110	4 yr	15 0	14 3		12 8	1 5
43	22	M	5	9	139	150/100	1 yr	12 6	12 1		11 5	1 6
86	66	F	5	7	100	190/ 90	2 yr	12 5	12 0		10 1	1 9
92	43	M	6	1	206	180/110	?	14 5	14 5		14 0	0 5
97	43	F	5	0	115	155/125	?	12 5	11 2		10 4	0 8
16	60	F	5	3	106	170/ 90	?	10 2	10 1		10 3	0 2
94	55	F	5	8	177	155/ 90	?	13 5	13 0		12 4	0 6

TABLE 3—*Size of Heart in Women*

Seventeen Obese Women												
Case	Age	Sex	Height		Weight, Lb	Average Blood Pressure	Known Duration	One Half Chest Diam eter, Cm	Actual Trans verse Cardiac Diameter, Cm	Enlarge ment, Cm	Predicted Trans verse Diam eter, Cm	Enlarge ment, Cm
			Ft	In								
35	49	F	5	4	195	200/130	8 yr	11 7	14 9	3 2	13 2	1 7
37	45	F	5	3	165	180/110	9 mo	11 7	13 1	1 4	12 2	0 9
40	61	F	5	5	213	210/110	?	12 0	13 5	1 5	14 1	-0 6
54	67	F	4	9	167	170/ 90	?	11 0	15 3	4 3	12 6	2 7
55	56	F	5	7	158	150/ 75	?	11 5	13 0	1 5	11 8	1 2
60	64	F	5	2	174	210/120	?	10 7	12 2	1 5	12 7	-0 5
76	59	F	5	10	195	160/110	10 yr	12 0	14 1	2 1	13 1	1 0
77	41	F	5	11	177	155/115	3 yr	12 5	13 8	1 3	12 2	1 6
90	55	F	5	0	158	200/100	8 yr	10 5	13 5	3 0	12 2	1 3
94	55	F	5	8	177	155/ 90	?	13 5	13 0	-0 5	12 4	0 6
100	70	F	4	10	165	155/ 70	?	10 4	13 4	3 0	12 7	0 7
101	46	F	5	6	191	200/100	?	11 4	13 6	2 0	12 6	1 0
6	70	F	5	7	170	180/ 90	?	11 6	13 0	1 4	12 4	0 6
12	59	F	5	6	174	180/110	10 yr	9 9	12 0	2 1	12 5	-0 5
29	52	F	5	5	165	180/ 90	?	11 0	11 9	0 9	12 2	-0 3
63	70	F	5	6	175	150/ 90	?	12 5	13 2	0 7	12 7	0 5
32	58	F	5	2	220	150/ 85	?	12 0	12 9	0 9	14 3	-1 4
Average									18 ± 0 03		07 ± 0 02	
Nine Underweight Women												
16	60	F	5	3	106	170/ 90	?	10 2	10 1	-0 1	10 3	0 2
49	59	F	5	4	119	160/100	5 yr	11 2	12 0	0 8	10 5	1 5
59	60	F	5	0	92	220/ 90	?	9 7	11 7 5	2 0	9 9	1 8
86	66	F	5	7	100	190/ 90	2 yr	12 5	12 0	-0 5	10 1	2 4
97	43	F	5	0	115	155/125	?	12 5	11 2	-1 3	10 4	0 8
102	26	F	4	11	101	150/ 85	2 yr	10 2	9 0	-1 2	9 9	-0 9
3	62	F	5	3	106	160/100	12 yr	13 5	15 0	1 5	10 3	4 7
41	75	F	5	2	106	180/115	?	13 5	14 4	0 9	10 4	4 0
46	60	F	5	5	117	175/ 90	4 mo	12 0	13 0	1 0	10 5	2 5
Average									0 34 ± 0 1		19 ± 0 1	

of Hodges and Eyster tending to show larger hearts (average  $1.9 \text{ cm} \pm 0.1$ ) than the Danzer ratio (average,  $0.34 \text{ cm} \pm 0.1$ ). This makes it apparent that the large number of overweight persons in our series, as compared with Bainton's patients, who were preponderantly underweight or of normal weight, is the factor causing the discrepancy.

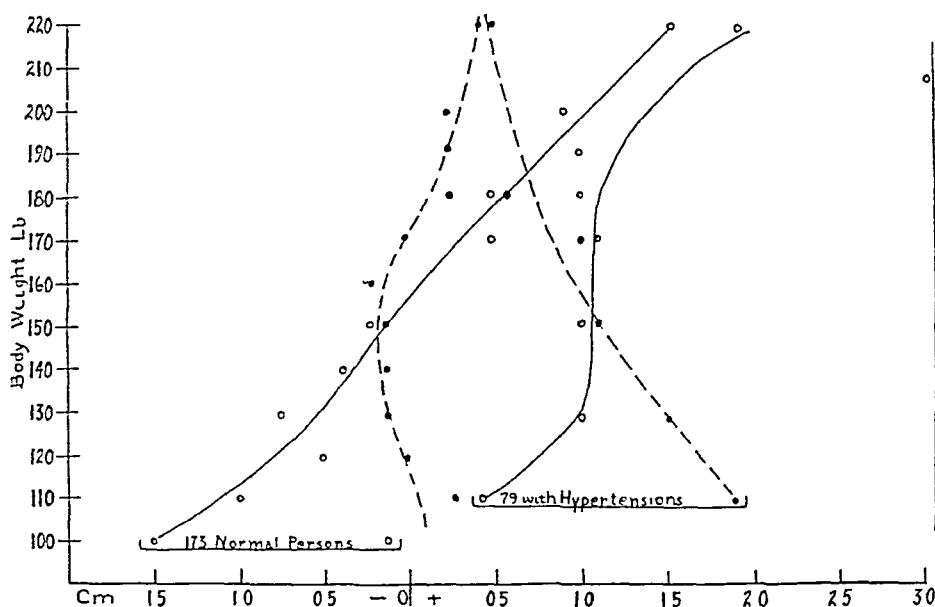
TABLE 4—*Size of Hearts of Subjects with Hypertension*

Twenty Three Men												
Case	Age	Sex	Height		Weight, Lb	Average Blood Pressure	Known Duration	One Half Chest Diam eter, Cm	Actual Trans verse Cardiac Diameter, Cm	Enlarge ment, Cm	Predicted Trans verse Diam eter, Cm	Enlarge ment, Cm
			Ft	In								
1	54	M	5	8	174	200/110	1 yr	13.0	14.0	1.0	13.1	0.9
2	54	M	5	7	165	210/130	3 yr	15.0	16.5	1.5	12.9	0.6
4	74	M	6	2	173	170/ 85	?	16.5	18.0	2.0	13.1	0.9
5	45	M	6	0	200	210/140	2 yr	14.2	18.0	3.8	13.8	4.2
15	56	M	5	8	145	190/110	8 yr	12.7	13.0	0.3	12.1	0.9
19	37	M	5	5	135	165/120	5 mo	12.1	11.6	-0.4	11.6	0.1
22	57	M	5	7	150	180/130	12 yr	12.7	14.5	1.8	12.3	2.2
25	55	M	5	9	144	175/ 95	17 yr	11.7	13.5	1.8	12.0	1.5
34	63	M	5	6	195	170/110	?	14.0	18.5	4.5	14.2	4.3
45	65	M	5	10	150	150/ 90	?	12.2	12.5	0.3	12.2	0.3
53	64	M	5	8	170	160/100	?	11.7	14.0	3.3	13.1	0.9
57	69	M	5	4	160	165/ 95	?	13.0	12.0	-1.0	12.0	-0.9
65	72	M	5	9	179	190/110	24 yr	16.0	16.2	0.2	13.5	2.7
66	62	M	5	8	170	170/ 90	8 yr	11.7	13.0	1.3	11.2	1.8
72	72	M	5	6	157	210/130	7 mo	13.0	14.5	1.5	12.8	1.7
78	58	M	5	7	133	200/105	7 yr	11.5	13.5	2.0	11.6	1.9
79	64	M	5	8	170	160/100	?	11.7	14.0	2.3	13.1	0.9
80	74	M	5	11	154	150/ 60	2 yr	13.0	12.0	-1.0	12.5	-0.5
83	67	M	6	0	165	260/150	?	12.1	16.6	4.5	12.7	3.9
95	50	M	5	7	164	170/100	?	12.5	11.8	-0.7	12.8	-1.0
99	56	M	5	10	195	180/140	2 yr	15.0	17.2	2.2	13.8	3.4
104	62	M	5	6	133	180/ 95	4 yr	11.7	11.9	0.2	11.8	0.1
105	58	M	5	9	203	170/100	10 yr	13.0	15.2	2.2	14.6	0.6
Twenty Two Women												
11	79	F	5	6	124	230/ 90	10 yr	13.0	14.5	1.5	10.8	3.7
20	78	F	5	1	134	210/ 80	18 yr	11.5	12.5	1.0	11.4	1.1
26	46	F	5	8	125	170/120	4 yr	10.5	10.8	0.3	10.5	0.3
28	56	F	5	6	143	190/110	10 yr	11.0	11.8	0.8	11.3	0.5
30	41	F	5	0	121	140/ 85	10 yr	11.3	12.7	1.5	10.7	2.0
42	68	F	5	2	148	230/130	15 yr	11.7	13.5	1.8	11.7	1.8
51	72	F	5	2	121	160/ 85	?	10.2	12.8	2.6	10.9	1.9
56	60	F	5	2	130	180/100	?	11.0	11.0	0.0	11.1	-0.1
62	74	F	5	2	142	155/ 85	?	11.2	13.3	2.1	11.7	1.6
64	64	F	4	10	121	170/100	?	9.8	11.7	1.9	10.9	0.8
67	60	F	5	0	130	170/ 90	8 yr	11.7	13.0	1.3	11.2	1.8
70	65	F	5	2	131	245/ 90	?	11.6	14.6	3.0	11.2	3.4
74	58	F	5	2	127	160/ 75	2 yr	11.1	12.8	1.7	10.9	1.9
82	51	F	5	4	146	190/130	1 yr	11.0	12.0	1.0	11.5	0.5
84	50	F	5	7	132	215/130	15 yr	13.0	13.5	0.5	10.8	2.7
87	43	F	5	6	124	170/100	?	10.9	11.7	0.8	10.5	1.2
89	34	F	5	6	129	220/140	?	11.5	12.1	0.6	10.6	1.5
91	50	F	5	3	130	220/120	10 yr	10.0	11.5	1.5	11.0	0.5
93	69	F	5	2	142	200/100	?	12.2	14.5	2.3	11.6	2.9
96	68	F	5	2	123	190/100	5 yr	9.2	12.2	3.0	10.7	1.5
103	25	F	5	6	142	150/100	6 mo	13.0	10.4	-2.6	10.9	-0.5
106	54	F	5	3	125	160/ 90	?	11.0	11.4	0.4	10.8	0.6

in results in the application of the standards in the two groups of subjects. The influence of body weight on the results obtained by the cardiothoracic ratio and by the prediction figures may be expressed graphically. In the chart the divergence in heart size from the predicted normal, expressed in centimeters, has been plotted against the body weight in pounds. The dots and circles representing an average value



for all persons at the weight indicated on the ordinate have been connected by smoothed curves. The data for persons without heart disease have been derived from Bainton's figures. There is a pronounced degree of correlation between the cardiothoracic index and the body weight in these persons, such that thin persons will have, according to this standard, hearts smaller than normal, whereas obese persons will have a cardiothoracic ratio placing them definitely in the group with cardiac enlargement. This correlation, as one might expect, is not as evident in the series of subjects with hypertension, but sufficiently definite to warrant the conclusion that the Danzer ratio is of little value in defining cardiac enlargement in thin persons.



Effect of body weight on the divergence from predicted normal transverse cardiac diameters. The broken line with the solid dots give the prediction figures and the unbroken line with the open circles the figures based on the cardiothoracic index.

That body weight, however, does not influence appreciably the criterion of normal by the prediction figures in the heart size of persons without heart disease, but apparently alters the results when applied to persons with hypertrophied hearts, is likewise evident. By this standard, thin persons with hypertension show the greatest cardiac enlargement, and obese persons, little or no enlargement. That this is not true is shown in table 5, in which are listed, in descending order of heart weight, the essential data, with the results obtained by the two standards under discussion, for 14 patients who came to autopsy and on whom orthodiagrams had been made a short time previously. Seven additional patients are listed in table 6, in whom the heart size was studied by means of a roentgen-ray plate made at a distance of 2 meters.

Attention is called to patient A H, with a heart weight of 720 Gm and to patient J D, with a heart weight of 530 Gm. The standard of Hodges and Eyster failed to show enlargement. Both patients were obese. It may be concluded that the prediction figures are not trustworthy as a guide to abnormal heart size in the presence of obesity. From the data at hand, we are not prepared to say why this is so, unless it is that the high position of the diaphragm in obesity displaces the

TABLE 5—*Weight of Hearts of Fourteen Patients Previously Studied by Orthodiagraphy*

Name	Sex	Age	Diagnosis	Weight, Lb	Height		Weight of Heart, Gm	One Half Chest Diam- eter, Cm	Actual Transverse Cardiac Diam- eter by		En- large- ment, Cm	Pre- dicted Trans- verse Diam- eter, Cm		En- large- ment, Cm
					Ft	In			Ortho- dia- gram, Cm					
J E	M	81	Hypertension, con- gestive heart failure	152	5	6	760	14.1	17.4	3.3	12.4		5.0	
A H	M	71	Hypertension, angina pectoris, congestive heart failure	220	5	2	720	12.0	12.9	0.9	14.7		-1.8	
A C	F	67	Hypertension, con- gestive heart failure	142	5	2	650	12.0	14.5	2.5	11.0		3.5	
R L	M	54	Coronary sclerosis, angina pectoris	165	5	7	678	12.0	14.8	2.8	12.4		2.4	
S E	M	44	Aortic regurgitation, carcinoma of pancreas	146	5	9	540	13.0	13.0	0.0	11.6		1.4	
F L	M	75	Hypertension, coro- nary occlusion	156	5	6	530	13.5	15.7	2.2	12.2		3.5	
A B	M	67	Coronary sclerosis, angina pectoris	120	5	5	530	11.0	13.8	2.8	10.9		2.9	
J D	F	61	Hypertension, lobar pneumonia	213	5	5	530	12.0	13.5	1.5	13.6		-0.1	
J H	M	50	Carcinoma of bron- chus	175	6	1	470	15.0	12.7	-2.3	12.5		0.2	
G B	M	72	Hypertension, coro- nary occlusion	170	5	8	440	13.2	13.2	0.0	12.6		0.6	
S R	M	39	Malignant hyperten- sion, uremia	144	5	10	430	12.7	15.7	3.0	11.5		4.2	
S D	F	56	Primary pulmonary sclerosis	119	4	11	400	10.5	13.7	3.2	10.3		3.4	
J W	M	64	Hypertension, aortic regurgitation, carci- noma of pancreas	159	5	7	340	13.0	15.7	2.7	12.2		3.5	
I S	M	68	Hypertension, gener- alized arteriosclerosis	170	5	6	280	15.4	13.8	-1.6	12.6		1.2	

cardiac apex outward, so that the greatest transverse cardiac diameter will bisect the apex tip itself instead of running through a point several centimeters above it on the left border, as in a normally placed heart. Likewise, the left ventricle may be rotated somewhat posteriorly. As a result of these two factors superimposed left ventricular enlargement might not manifest itself by a detectable additional increase in the measurement as it would in a "drop" heart, for instance, in which the line of measurement passes through a point well up on the wall of the left ventricle which itself lies more anteriorly.

*Correlation with Electrocardiographic Observations*—Electrocardiograms were made of 73 patients of our series. Forty-four (60.2 per cent) had a left axis deviation, 1 of whom (1.2 per cent) had no cardiac enlargement by the Danzer ratio. Four (9 per cent) had no enlargement by the prediction figures, while 5 (11.3 per cent) had a transverse cardiac diameter within the normal limits by both methods. One patient had a right axis deviation and a normal heart size by the Danzer ratio, but an enlargement of 2.7 cm by the Hodges and Eyster standard. Of the remaining 28 patients with no axis deviation, the Danzer ratio and the prediction figures each showed abnormal enlargement in 3 patients, while 23 (82.1 per cent) of the group had enlarged hearts by both methods. The two standards, then, were in close agreement throughout, but both failed to correlate closely with the elec-

TABLE 6—*Weight of Hearts of Seven Patients Previously Studied by Roentgenography*

Name	Sex	Age	Diagnosis	Weight, Lb	Height		Weight of Heart, Gm	One Half Chest Diam eter, Cm	Actual Trans verse Cardiac Diam eter, Cm	En large ment, Cm	Predicted	
					Ft	In					Trans verse Diam- eter, Cm	En large ment, Cm
H L	F	30	Carcinoma of pancreas	124	5	2	200	12.0	11.0	-1.0	10.5	0.5
A F	F	53	Carcinoma of breast	100	5	0	210	12.1	12.4	0.3	9.8	2.6
M G	F	60	Carcinoma of pancreas	121	5	4	260	14.7	12.5	2.2	10.7	1.8
H F	M	54	Miliary tuberculosis	154	5	10	350	13.5	10.5	-3.0	12.3	-1.2
J W	M	44	Carcinoma of pleura	195	6	2	370	15.5	15.0	-0.5	13.6	-1.4
L H	F	54	Mitral stenosis	104	5	0	420	13.1	22.8	9.7	10.2	12.6
R F	M	48	Fibrosis of myocardium	180	5	9	570	16.0	19.0	3.0	13.3	5.7

tiocardiographic observations. However, the data more truthfully demonstrate the well known fact that the electrocardiographic evidence of ventricular enlargement is often lacking in the presence of definite hypertrophy and/or dilatation. The correlation with the electrocardiogram is too indefinite to be of value in judging the efficacy of any cardiac measurement proposed as a guide to define the normal size of a heart.

#### SUMMARY AND CONCLUSIONS

The ratio of the transverse cardiac diameter to the internal diameter of the chest (Danzer ratio), as determined by orthodiagraphy, was compared with the predicted normal cardiac diameters of Hodges and Eyster in 175 persons without heart disease previously reported on and in 79 persons with arterial hypertension.

A direct correlation was found between the cardiothoracic ratio and the body weight in persons both with and without potential cardiac

enlargement, such that thin persons tended to have transverse cardiac diameters less than one half the internal diameter of the chest, and obese persons had cardiac diameters greater than this by more than the experimental error of the determination.

The predicted diameters of Hodges and Eyster, while approaching more closely the actual diameters found in persons without cardiac enlargement, failed to disclose the presence of left ventricular enlargement in obese persons, but were a satisfactory guide in normal or underweight subjects. It is suggested that this is not the fault of the standard per se, but is due to the failure of left ventricular enlargement, through mechanical causes, to manifest itself by a detectable increase in the transverse diameter of the heart in obesity.

Both methods failed to demonstrate enlargement in 20.2 per cent  $\pm$  8.5 of 79 persons who presumably had cardiac hypertrophy.

These conceptions regarding the efficacy of the two standards were corroborated by the study of a series verified at autopsy.

A comparison of the incidence of cardiac enlargement, as defined by these standards, with the occurrence of left axis deviation in the electrocardiogram showed that the correlation is too indefinite to be of value in judging the relative efficacy of such measurements proposed for the detection of cardiac enlargement.

# Progress in Internal Medicine

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## DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

RUSSELL M WILDER, PH D, MD

AND

DWIGHT L WILBUR, MD

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Into the subject "disease of metabolism" there now come not only diabetes, gout, obesity and a few other conditions involving chemical abnormalities of the body fluids, as formerly, but disturbances of the glands of internal secretion which affect the metabolic processes and disorders of nutrition which result from the lack in the food of adequate quantities of vitamins and other food factors. The desirability of the broader concept of the subject has been made apparent by the recent identification and separation, in many cases in pure crystalline form, of several of the hormones and vitamins. This has brought a fuller realization that the chemical reactions that constitute the metabolic process are dependent on the presence in suitable quantities of these specific catalysts. An instance in point is furnished by the recent rapid advancement of the knowledge of the physiology of the anterior lobe of the pituitary body. The new knowledge bears on carbohydrate metabolism and diabetes more decisively than anything that has been done in the field of carbohydrate metabolism since the isolation and discovery of insulin.

## PROGRESS IN THE STUDY OF METABOLISM

HORMONES OF THE PITUITARY AND SUPRARENAL BODIES  
IN THE METABOLISM OF CARBOHYDRATE

That the metabolism of carbohydrate is in some way dependent on the function of the anterior lobe of the pituitary body, long suspected because of the relatively high incidence of acromegaly among patients suffering from diabetes, was dramatically revealed by the demonstrations of Houssay and his associates. After removing the pituitary body from frogs and from dogs, the removal of the pancreas was not followed by the usual degree of diabetes, indeed, some of the depancreatized animals showed no sugar in the urine and no hyperglycemia.

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From the Division of Medicine, the Mayo Clinic

Important information on the relationship between the pituitary body and carbohydrate metabolism is provided in a series of articles recently published by H. Lucke and his associates in Göttingen. The experiments were conducted on dogs.

The presence of a blood sugar-raising factor in extracts of the anterior lobe of the pituitary body, as indicated previously by the work of Houssay and Biasotti, Evans and others, was confirmed. Lucke preferred to call the factor "contra-insular hormone." The preparation he has used is a commercial preparation containing among other factors the blood sugar-raising principle (pancreophyson) supplied by the chemical firm Promonta of Hamburg. When given subcutaneously to normal dogs in doses from 5 to 10 cc. it produced a very slight elevation of the blood sugar, when given to dogs that had pancreatic diabetes it caused a marked increase of the hyperglycemia, and when given to dogs with pancreatic diabetes treated with insulin it produced hyperglycemia and increased the total excretion of dextrose. The effect, seemingly, was to counteract or to neutralize the action of insulin in lowering the level of the blood sugar.

In the regulation of the level of the blood sugar, the liver with its store of glycogen occupies the center of the stage as the effector organ. The pituitary hormone might reach the liver by way of the blood, either directly or indirectly, that is, it might act on the liver itself or on some gland of internal secretion, the secretion of which in turn would act on the liver. The thyroid gland and the suprarenal body might fall into this category of secondary order since both are included in the circuit of the blood and since the secretions of both have known effects on the store of glycogen of the liver. However, the peculiar anatomic relationship of the pituitary body to the central nervous system makes it necessary to consider a path of action which avoids the blood stream. The hormone might enter the cerebrospinal fluid through the stalk of the pituitary body and thereby stimulate the "sugar centers" in the brain stem or it might reach these centers by way of the blood. In either case the centers in question would be irritated, and nervous impulses could proceed by way of efferent sympathetic tracts and nerves to the primary or secondary effector organs involved. In this case the final effect, namely, glycogenolysis, likewise could be accomplished either directly, by the stimulation of the liver, or indirectly, by the stimulation of the thyroid gland or the suprarenal bodies. The possibility of nervous inhibition of the mechanism of the pancreas for the production of insulin, which would result in hyperglycemia, was not under consideration, because the hormone in the type of experiment conducted by Houssay is demonstrably active in the absence of the pancreas.

The possible intervention of the thyroid gland was an especially important question because of hormonal relationships previously recognized between the pituitary body and the thyroid gland and because of the well known influence of the hormone of the thyroid gland on the tolerance for dextrose of patients with diabetes. Lucke and his associates<sup>1</sup> found (1) that the injection of a highly purified thyrotropic hormone did not elevate the blood sugar (this observation had previously been made by others), (2) that the effect of the blood sugar-raising hormone on the level of the blood sugar was much more immediate and of much greater intensity than the effect obtainable with thyroxine, and (3) that the effect of the blood sugar-raising hormone was not diminished by the previous removal of the thyroid gland. It was concluded that the blood sugar-raising hormone is wholly distinct from the thyrotropic hormone and in its action on the blood sugar does not involve the intermediation of the thyroid gland.

The possibility of intervention by the suprarenal glands was then investigated.<sup>1c</sup> These organs could be stimulated either by the blood sugar-raising hormone in the blood or indirectly by way of the central nervous system. The observations were as follows: 1. The hypersensitivity to insulin of suprarenalectomized animals was confirmed. Incidentally, attention is directed to the evidence reviewed by Grafe<sup>2</sup> which indicates a balanced relationship between the suprarenal glands and the pancreas, an increased supply of epinephrine stimulating greater release of insulin and vice versa. It has also been shown by LaBarre and Houssa<sup>3</sup> that the uncontrolled hyperglycemia of the dog with pancreatic diabetes is accompanied by a lowered secretion of epinephrine, that the administration of insulin under such circumstances stimulates the release of more epinephrine and that the administration of sugar again suppresses the activity of the suprarenal glands. According to LaBarre these effects are accomplished by the irritation of the sugar centers in the brain stem. The hypersensitivity to insulin which is observed in suprarenalectomized animals is attributed by Lucke to the loss of power to respond to the injection of insulin with the release of epinephrine.

2. The blood sugar-raising hormone in Lucke's experiments was without effect in raising the level of the blood sugar of suprarenalec-

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1 Lucke, H., Heydemann, E. R., and Duensing, F. Untersuchungen über den Wirkungsmechanismus des kontrainsularen Hormons des Hypophysenvorderlappens. (a) I. Hypophysenvorderlappen, Schilddrüse und Kohlehydratstoffwechsel, *Ztschr. f. d. ges. exper. Med.* **91** 106, 1933, (b) II. Hypophysenvorderlappen, Nebenniereninsuffizienz und Kohlehydratstoffwechsel, *ibid.* **91** 483, 1933, (c) III. Hypophysenvorderlappen, Nebennierenentnervung und Kohlehydratstoffwechsel, *ibid.* **91** 492, 1933.

2 Grafe, E. Ueber die Regulation der Insulinabgabe, *Med. Klin.* **28** 469 (April 1) 1932.

3 LaBarre, J., and Houssa, P. Diabète et adréalinésécration, *Ann. de physiol.* **8** 340, 1932.

tomized dogs, and it was concluded that the activity of the anterior lobe of the pituitary body in carbohydrate metabolism depends on the presence of a functionally efficient suprarenal mechanism, that the path of action of the hormone must be by way of the suprarenal glands, and that the end-result, or the hyperglycemia, depends on a discharge of epinephrine.

There remained the problem as to how the suprarenal bodies were stimulated by the hormone in question, whether by way of the blood stream or by a primary stimulation of the sugar centers in the brain stem. In the next experiments the nerve connections of the suprarenal glands of dogs were completely severed, which lowered the blood sugar level after fasting to 10 or 15 mg per hundred cubic centimeters below the normal level and sensitized the animals to injections both of epinephrine and of insulin. Such animals were completely unaffected by injections of the blood sugar-raising hormone. The blood vessels to the suprarenal glands had been preserved, so it appears that the hormone in question does not affect the suprarenal glands through the blood stream but that its action is central, related to the suprarenal glands by nerve paths.

This does much to explain why animals deprived of suprarenal glands or with denervated suprarenal glands behave, with respect to their carbohydrate metabolism, like animals with insufficiency of the pituitary body, showing the same tendency to hypoglycemia and the same hypersensitiveness to insulin. In this connection stands the interesting observation of Viale<sup>4</sup> and of Long and Lukens<sup>5</sup>. The latter investigators, by making use of extracts of the cortex of suprarenal glands, were able to remove the suprarenal glands and the pancreas of cats, thereby obtaining animals like those of Houssay and Biasotti, with no glycosuria and relatively little hyperglycemia. It is evident that the suprarenal glands play a considerably larger rôle in carbohydrate metabolism than has been attributed to them heretofore, this being subject, however, to regulation by the anterior lobe of the pituitary body.

The next step taken by Lucke and his associates was to determine whether the blood sugar-raising hormone of the pituitary body reached the sugar centers in the brain stem by way of the blood stream or through the pituitary stalk and the cerebrospinal fluid. The active extract was injected into the cerebrospinal fluid through a suboccipital puncture. The procedure was almost painless and could be performed

4 Viale, Gaetano. Die Bedeutung der Nebennierenrinde für den Stoffwechsel der Kohlehydrate, *Klin. Wchnschr.* **12** 467 1933.

5 Long, C. N. H., and Lukens, F. D. W. Observations on Adrenalectomized, Depancreatized Animals, *J. Clin. Investigation* **13** 685 (July) 1934.



without resorting to narcosis and without constraining the animal. These are important considerations when the concentration of blood sugar is involved. It was found that when administered to normal dogs in this way, the hormone had an intense and prolonged effect, even in doses only one-tenth as large as those necessary to obtain results by subcutaneous or intravenous injection. In illustrative charts the blood sugar level is shown to rise almost immediately to a high point of about 70 mg per hundred cubic centimeters above the basal level and to maintain a considerable elevation for as long as six hours. Control injections of pituitary extract, inactivated by heating, and of physiologic solution of sodium chloride produced relatively slight elevation of the blood sugar concentration. The conclusion was reached that the hormone normally is carried to the blood sugar centers and the brain stem by way of the cerebrospinal fluid. Also it was found that the hyperglycemia produced by suboccipital injection of the blood sugar-raising hormone could be checked immediately by blocking the sympathetic nervous system with a large intramuscular injection of ergotamine. Ergotamine in dogs ordinarily produces a slight depression of the blood sugar level of not over 20 mg per hundred cubic centimeters. In the animals that had received the blood sugar-raising hormone by suboccipital injection, the blood sugar level of about 170 mg per hundred cubic centimeters was almost instantly depressed below 100 mg, and after a lapse of two or three hours, as the effect of the ergotamine wore off, the blood sugar level again began to rise. The influence of general narcosis was similar. A narcotic was selected for the brain stem which has relatively little effect on the blood sugar. In a dog given 20 cc of the blood sugar-raising hormone there developed unmistakable hyperglycemia, and the blood sugar level was promptly lowered by the intravenous injection of 0.4 Gm of a barbituric acid derivative per kilogram of body weight. In another experiment a like dose of the barbituric acid derivative was given first, and after the blood sugar level had come to rest 5 cc of the blood sugar-raising hormone was injected into the cerebrospinal fluid. This dose of the hormone was five times as large as would be required otherwise to cause marked hyperglycemia, yet the blood sugar level fell steadily for the following six hours. It was concluded that the functional efficiency of the brain and of the sympathetic nerve paths connecting the sugar centers and the suprarenal glands is essential for the exercise by the anterior lobe of the pituitary body of its regulative control of the blood sugar-raising activity of the suprarenal medulla. Of significance in this connection is the recent observation of Davis and his associates<sup>6</sup> that cats with experimental

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6 Davis, Loyal. The Relation of the Hypophysis, Hypothalamus, and the Autonomic Nervous System to Carbohydrate Metabolism, *Ann Surg* **100** 654 (Oct) 1934

lesions accurately placed in the diencephalon withstand pancreatectomy without having severe diabetes develop. The pituitary body is not injured by the operation. The lesions, produced by means of the Horsley-Clark stereotomic instrument, were bilateral and were situated in the tuber cinereum, "slightly rostro-dorso-lateral to the mammillary bodies at the level of the ventro medial hypothalamic nucleus." The cats had a high content of blood sugar, but could be maintained for long periods of time without exhibiting the symptoms usually observed after ablation of the pancreas. It is to be supposed that they would be resistant to suboccipital injections of the blood sugar-raising pituitary extracts, but so far as we know, this crucial experiment has not as yet been done.

In their next article Lucke and his associates<sup>7</sup> showed that the blood sugar-raising factor, if injected into the muscles, is secreted into the spinal fluid. From thirty to one hundred and twenty minutes after 20 cc of the hormone was given to a dog by intramuscular injection, as little as 2 cc of the spinal fluid of the dog injected into a normal rabbit was enough to provoke a marked elevation of the blood sugar level. The authors referred to the evidence compiled by Trendelenburg<sup>8</sup> which indicates that other pituitary hormones pass into the cerebrospinal fluid. The amount of blood sugar-raising hormone in the fluid is too small under normal conditions to permit its recognition, but the authors suggested that fluid containing demonstrable amounts of this hormone might be found in acromegalic patients with diabetes. This is to be watched for.

The general conclusions arrived at by Lucke are summarized as follows. Contrainsular hormone (the blood sugar-raising hormone) is formed in the anterior lobe of the pituitary body. The substance has not been identified chemically, but it possesses unmistakable biologic properties. It is certainly not identical with the gonadotropic and thyrotropic hormones, but thus far it has not been separated from the growth hormone. It is distinguished from the pituitary hormone of fat metabolism of Anselmino and Hoffmann<sup>9</sup> by filtration. Like the Anselmino hormone it promotes an increase of acetone in the blood and is found in association with the gonad-stimulating hormone, but unlike the Anselmino hormone it is not ultrafiltrable. The blood sugar-raising factor of the pituitary body is secreted into the cerebrospinal fluid and under special conditions can be demonstrated biologically in the fluid.

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7 Lucke, H., and Hahndel, H. Untersuchungen über den Wirkungsmechanismus des kontrainsularen Hormons des Hypophysenvorderlappens. VI. Die Möglichkeit eines biologischen Nachweis des Kontrainsularen Hormons im Liquor cerebrospinalis, *Ztschr f d ges exper Med* **91** 704, 1933.

8 Trendelenburg, Paul. *Die Hormone, ihre Physiologie und Pharmakologie* Vol 1. Keimdrüsen. Hypophyse. Nebennieren, Berlin, Julius Springer, 1929.

9 Anselmino, K. J., and Hoffmann, Friedrich. Die Ursachen des Icterus Neonatorum, *Klin Wchnschr* **10** 97 (Jan 17) 1931.

Its immediate action is on the sugar centers of the brain stem. Consequently, it is ineffective when these centers are neutralized by pharmacologic means (or destroyed by experimental lesions?). In turn, under the influence of the hormone, the brain centers activate the suprarenal glands, the stimulation passing from the centers to the suprarenal glands by way of the sympathetic nervous system. For this reason the action of the pituitary hormone is interrupted by pharmacologic or mechanical inhibition of the respective sympathetic nerve fibers as well as by extirpation of the suprarenal glands. The thyroid gland is not involved. The end-effect, elevation of the level of the blood sugar, is a result of the release of epinephrine, but the anterior lobe of the pituitary body and not the suprarenal glands is the regulator.

The possible application of these observations to the treatment of diabetes is discussed by Lucke<sup>10</sup> in a later article. The surgical removal of one suprarenal body is followed by no evidence of suprarenal insufficiency and therefore can be of no significance therapeutically. Bilateral suprarenalectomy is out of the question because of its fatal consequences. Rupp<sup>11</sup> demonstrated in 1925 that section of the splanchnic nerves in animals exaggerated the effect of insulin in lowering the level of blood sugar. Cesa-Bianchi and Moretti<sup>12</sup> observed some depression of the blood sugar concentration of diabetic patients after treatment with ergotamine, but the dose of ergotamine necessary for this is in the range of toxicity. Ciminata<sup>13</sup> in 1928 claimed to have cured pancreatic diabetes in animals by sectioning the suprarenal nerves. This was disputed by Nothmann,<sup>14</sup> who pointed out that the protocols presented by Ciminata indicated an incomplete pancreatectomy. Nevertheless, Ciminata has at least demonstrated the favorable influence of denervation of the suprarenal glands in a condition of partial diabetes. An improvement in the tolerance for dextrose after denervation of the suprarenal glands was observed by de Takáts and Cuthbert,<sup>15</sup> after resection of the celiac ganglion in dogs. Since then, de Takáts and Fenn<sup>16</sup> have described the clinical results of bilateral splanchnic section

10 Lucke, Hans. Stellt die Entnervung der Nebennieren eine aussichtsvolle Diabetesbehandlung dar? *Ztschr f klin Med* **125** 361, 1933

11 Rupp, F. Ueber den Einfluss des Nervensystems auf den Zuckergehalt des Blutes, *Ztschr f d ges exper Med* **44** 476, 1924-1925

12 Cesa-Bianchi and Moretti, quoted by Lucke<sup>10</sup>

13 Ciminata, A. Einfluss der Durchschneidung der Nebennieren auf den Diabetes mellitus, *Klin Wchnschr* **11** 150 (Jan 23) 1932

14 Nothmann, M. Einfluss der Durchschneidung der Nebennieren-Nerven auf den Diabetes mellitus, *Klin Wchnschr* **11** 774 (April 30) 1932

15 de Takats, G. and Cuthbert, F. P. The Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, *Am J Physiol* **102** 614 (Dec) 1932

16 de Takats, G., and Fenn, G. K. Bilateral Splanchnic Nerve Section in Juvenile Diabetes, *Ann Int Med* **7** 422 (Oct) 1933

in cases of diabetes in man. The results are encouraging in that much less insulin is necessary after the operation, but the procedure does not constitute a cure of the metabolic disorder nor does it permit the patient to do without insulin. The experiments of de Takats and those of J. M. Donald<sup>17</sup> are significant and support Lucke's conclusions that the impulse between the sugar centers in the brain stem and the liver is transmitted through the suprarenal glands. Neither de Takats nor Donald was able to detect any influence on the tolerance for dextrose from procedures which effected the denervation of the liver alone.

The bearing of this complex physiology on the conception of the pathologic physiology of diabetes and on the treatment of spontaneous diabetes in man is not entirely evident. A classic experiment of Claude Bernard established the significance of a "sugar center" in the medulla, and subsequent investigation has demonstrated other centers concerned with carbohydrate metabolism located in the diencephalon. The not infrequent occurrence of glycosuria following fracture of the base of the skull has long been a matter of common knowledge to physicians. This and the less frequent glycosuria accompanying tumor and other pathologic lesions of the brain has been attributed to irritation of these centers. However, the glycosuria which accompanies such lesions has in almost all cases been transitory and mild, differing markedly in these respects from diabetes mellitus. The frequency of association of acromegaly and diabetes is not as impressive as might be supposed from some reports. Occasionally authors place it as high as 40 per cent, but in other series it has not been over 7 per cent. A positive reaction to the test of sugar tolerance can sometimes be obtained in persons with no glycosuria, and, on the other hand, occasional cases have been described by Oppenheimer<sup>18</sup> and Lichtwitz<sup>19</sup> in which spontaneous recovery occurred from diabetes which was so severe as to threaten death in coma. Von Noorden<sup>20</sup> considered this question among others in a recent general lecture on diabetes. He admitted that diabetes associated with acromegaly is characterized by fluctuations in severity that seem not to be influenced by treatment, but he considered that the existence of a type of diabetes caused by a pituitary disturbance which is independent of disease or of abnormality of the insular system is highly improbable. It is necessary in connection with recent interest

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17 Donald, J. M. Studies on Carbohydrate Metabolism Following Denervation of the Liver, *Am J Physiol* **98** 605 (Nov.) 1931

18 Oppenheimer, Albert. Ueber das Wesen der Zuckerkrankheit bei Akromegalie, *Klin Wchnschr* **9.17** (Jan 4) 1930

19 Lichtwitz, L. Hypophysare Symptome und Hypophysenkrankheiten, *Verhandl d deutsch Gesellsch f inn Med* **42** 35, 1930

20 von Noorden, Carl. Zur funktionellen Pathologie und Therapie der Zuckerkrankheit, *Med Klin* **29** 39 (Jan 6) 1933

in the pituitary body to recall the studies of Borchardt<sup>21</sup> of Konigsberg who, in 1908, produced glycosuria and hyperglycemia by the injection of crude extract of the pituitary body of the horse and of man. Borchardt thought it possible that a continuous excessive secretion of a product of the pituitary body might produce lasting diabetes in the active stage of acromegaly and that arrest of the excessive secretion, as a result of later degeneration of the pituitary tumor, might account for the absence of urinary sugar in many patients with acromegaly.

There is no evidence to incriminate the pituitary body in cases of diabetes unassociated with acromegaly. E. J. Kraus<sup>22</sup> demonstrated changes in the pituitary body in the large majority of persons with diabetes, especially in younger persons, but there is nothing in his work to indicate that the lesion of the pituitary body was primary. Almost all the cases of young persons with diabetes which come to necropsy are cases of uncontrolled diabetes in which death resulted from diabetic acidosis. That the pituitary body under such circumstances should show evidence of degeneration cannot be accepted as evidence of primary disease of this organ.

Whether the course of diabetes can be modified by measures directed toward suppressing the activity of the pituitary body remains to be seen. Hutton<sup>23</sup> claimed to have obtained favorable therapeutic effects by the intensive roentgen irradiation of the pituitary body, but thus far no confirmatory observations have come to our attention. Another means of suppressing the activity of the anterior lobe of the pituitary body may be to administer large amounts of so-called female sex hormone. There seem to have been no reports of this in the clinical literature on diabetes, but Barnes and his associates,<sup>24</sup> who were among those to confirm the original experiments of Houssay and Biasotti, found that the administration of estrogenic substance to normal female dogs prevented all but mild glycosuria after pancreatectomy. When the injections of the estrogenic substance were discontinued the animals became severely diabetic, the resumption of the injections caused a reduction in the glycosuria. The authors issued a warning against the clinical application of this procedure until more

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21 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, *Ztschr f klin Med* **66** 332, 1908.

22 Kraus, E. J. Ueber Beziehungen der chromophilen Zellen der Hypophyse zum Kohlehydrat-, Fett- und Cholesterinstoffwechsel, *Med Klin* **29** 449 (March 31) 1933.

23 Hutton, J. H. Diabetes Mellitus and Essential Hypertension. A Theory as to Their Etiology and Treatment, *Illinois M J* **64** 539 (Dec) 1933.

24 Regan, J. F., and Barnes, B. O. The Relation of the Hypophysis to Experimental Diabetes, *Science* **77** 214 (Feb 24) 1933. Barnes, B. O., Regan, J. F., and Nelson, W. O. Improvement in Experimental Diabetes Following the Administration of Amniotin, *J A M A* **101** 926 (Sept 16) 1933.

of the effects of the estrogenic factor are known. Complete suppression of the pituitary body might be followed by the atrophy of other organs. This is especially true of the suprarenal cortex, which undergoes an involution when the pituitary body is removed.

#### HEREDITY IN DIABETES

Many students of metabolism, while impressed with the frequency of the incidence of diabetes in the parents and the siblings of diabetic patients, have been wary of accepting mendelian interpretations—and very properly so. The data are not of the sort that permit a forthright decision. The statistical analysis of such data must depend, for instance, on the age of the nondiabetic as well as of the diabetic members of the families examined, and few clinical records contain this information. An ideal genealogy would be that of a family in which every member had lived beyond the ninth decade, so that a complete opportunity for the expression of the disease had been given to every member. Pincus and White, from the laboratory of general physiology, Harvard University, and the Joslin Diabetic Unit of the New England Deaconess Hospital, respectively, have collected data which are undoubtedly superior to anything that has appeared before. The material consists of detailed family histories of 523 diabetic patients and control histories of a nondiabetic group, together with the analysis of a large group of cases from the clinic of Dr. Joslin and from other clinics. Also, twenty-three families were studied in which both parents had diabetes. Diabetes occurred ten times more frequently among the brothers and sisters of the persons with diabetes than it did among the control population, and the investigators concluded that the occurrence of diabetes among children of diabetic parents is in accord with the hypothesis that the potentiality for developing diabetes was inherited as a simple mendelian recessive. If this was correct, they expected to predict not only the number of offspring with diabetes in the twenty-three conjugal families but also the age at onset. This was accomplished. Their conclusions mean that when a diabetic person marries a diabetic person all the children are predestined to have diabetes, it will develop in 0.2 per cent in the first decade, in 3 per cent in the second, in 5 per cent in the third, in 10 per cent in the fourth, in 20 per cent in the fifth, in 30 per cent in the sixth, in 50 per cent in the seventh and in 60 per cent in the eighth. If a person with diabetes marries a carrier of potentiality to acquire diabetes one half of the offspring are predestined to have diabetes. If a carrier marries a carrier, one fourth of the children are predestined to have diabetes. But if a person with diabetes marries a person who has not diabetes, none of the children are predestined to have diabetes. Diabetic patients who wish to marry and have children

may do so provided the marriage is to a person who neither has diabetes himself nor is a carrier of the potentiality. Conversely, the marriage of two diabetic persons, which would be sure to result in diabetic children, must be avoided. The prevalence of diabetes in the Jewish race is probably accounted for on this basis. Not only must one train diabetic children to marry into families in which there is no trace of diabetes but, as pointed out by Pincus and White, one must also carry this instruction to the children of diabetic parents, for they represent true and insidious carriers of the disease. A study by L. R. Grote<sup>25</sup> led to similar conclusions. A diabetic taint was found in the families of 40 per cent of 457 persons with diabetes, and he recommended that the marriage of two persons with diabetes be forbidden by law or be permitted only on the condition that both parties be sterilized. The right to marry should be questioned if both come from diabetic families, even though neither actually has diabetes, and the permissibility of marriage between a diabetic person and a nondiabetic person should depend on the proof of the absence of diabetes in three generations of the blood relatives of the latter.

#### SYMPOSIUM OF THE NEW YORK ACADEMY OF MEDICINE

An unusually instructive series of lectures on the disorders of metabolism was held by the New York Academy of Medicine from Oct. 23 to Nov. 3, 1933. The total exchange of energy was the subject of a lecture by DuBois.<sup>26</sup> He referred therein to the relationship of the velocity of the blood flow and cardiac output to the total metabolism. The whole problem of the management of heart disease, as revealed with particular clarity by the studies of Blumgart,<sup>27</sup> Weiss and others, is linked with the demands of total metabolism, and the required cardiac output, with the capacity of the heart to meet the need. In conditions of congestive heart failure and coincidental pathologic states without clinical evidence of thyroid toxicity, benefit may be derived from lowering the basal metabolic level by total ablation of the thyroid gland.

The patient who was first subjected to this procedure was presented at the meeting by Dr. Blumgart and his associates. Previously bed-

25 Grote, L. R. Ueber die Vererblichkeit der Zuckerkrankheit, *Med. Klin.* **1** 185 (Feb. 9) 1934.

26 DuBois, E. F. Total Energy Exchange in Relation to Clinical Medicine, *Bull. New York Acad. Med.* **9** 680 (Dec.) 1933.

27 Blumgart, H. L., Riseman, J. E. F., Davis, David, and Berlin, D. D. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. The Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* **52** 165 (Aug.) 1933. Blumgart, H. L., Levine, S. A., and Berlin, D. D. Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* **51** 866 (June) 1933.

hidden, he was engaged in the exhibition hall in running the moving picture demonstration of the technic of the operation. He required a very small dose of thyroid extract to maintain his metabolic rate at the upper limit of the myxedema zone. The procedure is still on trial and is not to be hastily recommended. The surgical mortality is very high. The operation required involves the risk of injury to the recurrent nerves and to the parathyroid bodies. Louie,<sup>28</sup> fearful about the death rate if the operation becomes popular among less skilful surgeons, begs for a truce of at least two years in order to give time for a better evaluation of the results already obtained. He regards the results as being very questionable. A recent paper<sup>29</sup> from the Mayo Clinic relates the case of a man with diabetes mellitus who was treated by total thyroidectomy. The outcome, while of importance theoretically by showing that less insulin is required to support the carbohydrate metabolism when the basal metabolic rate is lowered, does not encourage the repetition of the operation for diabetes. The patient complained that sensitiveness to cold and the lack of endurance were so disturbing that the advantage of improved tolerance was not appreciated.

One of the outstanding features of diabetes consists in alterations of the water metabolism as indicated by the symptoms of polydipsia and polyuria. Himwich<sup>30</sup> reported the production of a temperature of 104 F (40 C) in diabetic dogs by withholding insulin and water. The fever was attributed to anhydremia. Coincident anoxemia was encountered in the muscles, with a resulting rise of the lactic acid content of the blood and changes in the electrocardiogram similar to those observed when there is an insufficient supply of oxygen to the heart. Starr and Fitz in 1924 and other writers subsequently have commented on the presence of an organic acid not comprised in the group of acetone bodies in the urine of patients with diabetic acidosis. The observations of Himwich revealed that the unknown acid is lactic acid. In the twenty-four hour specimens of urine of one of his dogs, the amount of lactic acid was 1,885 mg.

The lecture on acidosis and alkalosis by Van Slyke<sup>31</sup> is recommended for reading by those who have had difficulty in following the scientific literature on the subject. Excess of carbonic acid, deficit of carbonic acid, excess of alkali and deficit of alkali, their causes,

28 Louie, O. R. Is Total Thyroidectomy Rational as a Method of Treatment? *Canad. M. A. J.* **31**: 502 (Nov.) 1934.

29 Wilder, R. M., Foster, R. F., and Pemberton, J. deJ. Total Thyroidectomy in Diabetes Mellitus, *Endocrinology* **18**: 455 (July-Aug.) 1934.

30 Himwich, H. E. The Metabolism of Fever, with Special Reference to Diabetic Hyperpyrexia, *Bull. New York Acad. Med.* **10**: 16 (Jan.) 1934.

31 Van Slyke, D. D. Acidosis and Alkalosis, *Bull. New York Acad. Med.* **10**: 103 (March) 1934.



significance and rational treatment are discussed with extraordinary lucidity and without too great a demand on the reader's acquaintance with gas laws, equilibrations and dissociation curves

Diabetes was thoroughly considered in a round table conference engaged in by Woodyatt, White, Scott, Mosenthal and Geyelin<sup>32</sup> The papers should be read by all physicians engaged in the treatment of the disease, only a few of the high points can be mentioned here Woodyatt, in reviewing dietary trends, commented on the fact that an occasional diabetic patient may have carbohydrate added to his diet with actual advantage to his tolerance The metabolic data in one such case were presented It was pointed out that similar observations were probably the basis for the von Noorden "oatmeal cure," the Mossé "potato cure" and other carbohydrate "cures" Unfortunately, as von Noorden wrote, "there are relatively few cases in which the results are so surprisingly favorable" In 1911 Klempeier appears to have demonstrated that analogous results could be produced by the administration of dextrose, but during the early stages in Woodyatt's experiment the patient was excreting dextrose, and there was at all times an excess of dextrose in the body Although several hypotheses have been advanced to explain the phenomenon, it still presents an interesting problem for further investigation

In this connection Geyelin reported 40 cases of diabetes in which the patients had been treated with insulin and diets high in fat and low in carbohydrate They were subsequently given diets containing "normal" proportions of carbohydrate, protein and fat Twenty-six of them had values for blood cholesterol higher than normal before the change in diet was made In Geyelin's diets the proportion of carbohydrate to fat has been approximately  $3\frac{1}{2}$  1, but a few patients were found whose values for blood cholesterol did not return to normal limits until the proportion of carbohydrate to fat reached 4 1 It seemed to Woodyatt, as it has to many other physicians interested in this field, that the most effective diet is one in which the patient obtains the necessary number of calories with the lowest possible dose of insulin The general conclusion has been that while individual patients may do with relatively small doses of insulin on a diet containing 300 Gm or more of carbohydrate, the majority of these patients find insulin economy when more of their calories are provided by fat

Scott issued a timely warning against "giving too much insulin to our older diabetic patients" Nathanson, of the University of Minnesota, showed by necropsy in 100 cases of diabetes that "the incidence of coronary sclerosis is approximately six and one-half times greater in

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32 Woodyatt, R T , White, Priscilla, Scott, J R , Mosenthal, H O , and Geyelin, H R Round Table Conference on Diabetes Mellitus, Bull New York Acad Med 10 335 (June) 1934

diabetics than in nondiabetics" As it is known that a heart diseased by arteriosclerosis of its coronary arteries needs more dextrose to function properly than does the normal heart, it is wise to treat diabetic patients over 50 years of age as potential subjects for heart disease and to insure an adequate level of blood sugar at all times In other words, while 100 mg per hundred cubic centimeters of whole blood is an ample concentration of blood sugar for normal persons with a normal heart, or even for young diabetic patients with a normal heart, this may not be ample for older patients with diabetes

#### FACTORS INFLUENCING THE ACTIVITY OF INSULIN

Boller, Uiberrak and Falta<sup>33</sup> have recently reported the result of extensive studies bearing on the problem of resistance to insulin They demonstrated that the transfusion of 300 cc of blood from a normal donor who had recently received a breakfast containing carbohydrate produced in a diabetic recipient who was sensitive to insulin a sharp, if temporary, depression of the blood sugar level A similar result was obtained with blood from a diabetic donor sensitive to insulin who had received an injection of from 20 to 40 units of insulin The amount of insulin contained in the 300 cc of transfused blood was estimated as about 1.3 units Diabetic recipients of such transfusions who are resistant to insulin give a negative response, as would be anticipated, but, what is more important, the blood from diabetic donors who are resistant to insulin and who have received an injection of 40 units of insulin fails to produce any effect on diabetic recipients who are sensitive to insulin

It had previously been shown by the authors that the insulin injected into patients who were resistant to insulin was not lost by excretion in the urine It might be assumed that the injected insulin in such cases was anchored by the tissues, but if so it is not apparent why it should be inactive Therefore, the authors were led to the opinion that one or several antibodies are present in patients who are resistant to insulin and that these are responsible for the relative inactivity of injected insulin

The technic of these transfusions was not described in full, but the authors said that no anticoagulants were used and that precautions were taken to avoid disturbing the blood sugar level of the recipients by painful or psychic stimuli By patients who are sensitive to insulin the authors referred to those who, like depancreated dogs, (1) require a relatively small dose of insulin, (2) are thrown into hypoglycemic shock if more than enough insulin is given to equalize the dextrose

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<sup>33</sup> Boller, R., Uiberrak, K., and Falta, W. Ueber die humerale Natur der Insulinresistenz, *Wien Arch f inn Med* **25** 25 (June 20) 1934

available or if insulin is given without food, the "Radoslov procedure," and (3) excrete a large amount of dextrose in the urine when insulin medication is discontinued. The patients who are resistant to insulin and who are said by the authors to be encountered in rather large numbers (1) require excessively large doses of insulin, (2) can be given extra insulin, that is, insulin over and above the amount necessary to make the urine sugar-free, without showing the symptoms of insulin shock and (3) excrete relatively little dextrose when insulin medication is discontinued. This differentiation of diabetic patients into "insulin-sensitive" and "insulin-resistant" types is described elsewhere by Falta <sup>34</sup>

Also bearing on the question of the inactivation of insulin by the blood is a study by Burger and Kohl <sup>35</sup>. It had been demonstrated by them previously that insulin when injected into an animal after clamping off the arteries to the principal masses of muscles had very little effect on lowering the blood sugar level and that if after an hour the clamps were removed so that blood reached the muscles there still was no lowering of the blood sugar level, although a second injection of insulin produced a characteristic effect indicating that the muscles were still intact. The observation led to the supposition that insulin was destroyed by the blood, and in the present study this was found to be the case. Insulin in crystalline form lost its activity when added to blood in vitro and incubated at 37 C (98.6 F) for from one to several hours. The same change occurred in a similar experiment with serum. That the neutralizing effect of the blood serum was attributable to an enzyme-like factor was suggested by the fact that the "inactivation" of the blood or serum by heating destroyed its ability to neutralize insulin. It was further observed that the blood of patients with lymphatic or myeloid leukemia possessed a greater neutralizing effect than did the blood from patients with no leukemia and that blood taken from the same leukemic patients after the leukocyte count had been reduced by roentgen irradiation behaved no differently than blood from normal persons. The bearing of this on the relative resistance to insulin of diabetic patients with leukocytosis is apparent. We are unaware of reports on the resistance to insulin in cases of diabetes complicated by leukemia.

Bearing on this matter of the activity of insulin are the astonishing results of experiments on the influence of magnesium in carbohydrate metabolism, as reported by Hans Franke <sup>36</sup> of Breslau. It was found

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34 Falta, W. Insulin und Diabetes mellitus, Verhandl d Gesellsch f Verdauungs- u Stoffwechselkr **11** 124 (Oct) 1932

35 Burger, M., and Kohl, H. Ueber kristallinisches Insulin. V Ueber Inaktivierung des Insulins durch Blut, Arch f exper Path **174** 130, 1933

36 Franke, Hans. Magnesium und Kohlehydratstoffwechsel, Arch f exper Path **174** 727, 1934

that the intravenous injection, within an hour, of a solution of magnesium chloride or magnesium gluconate, in concentration such that the total supply represented 100 mg of magnesium, caused an increase in the glycogen of the liver to three or four times the amount normally present and no decrease, but a slight increase, in the glycogen of the muscles. Control injections of sodium chloride and of "phosphate solution" had no such effect, and injections of calcium chloride caused only a slight increase in the glycogen of the liver. When magnesium was injected together with epinephrine, the usual influence of epinephrine on both the muscle and the liver was missed, and the quantity of glycogen was increased to three or four times the normal amount both in the liver and in the muscle. The magnesium salts exerted similar effects when given by mouth.

#### EXERCISE AND THE BLOOD SUGAR LEVEL

It is commonly believed that exercise reduces the blood sugar level of diabetic patients. Richardson<sup>37</sup> determined the effect of a standard form of exercise in 61 cases of diabetes, finding that in mild cases, with a blood sugar level after fasting between a normal value and 175 mg per hundred cubic centimeters, a marked lowering of the blood sugar level was produced, but that in severe cases with the level ranging from 175 to 300 mg, a progressively marked elevation resulted. In the severe cases of diabetes the intravenous injection of 0.1 unit of insulin when given before a period of rest was without marked effect on the blood sugar value but when given before a period of exercise caused a marked drop in the blood sugar values. The comparison of the values for the mild and those for the severe cases suggests that in the former the difficulty was one of an inadequate, or inadequately available, glycogen reserve of the muscles and liver and that in the latter it was one of more or less complete inability to convert the dextrose of the blood to the needs of the tissues.

#### PURINE METABOLISM AND GOUT<sup>38</sup>

While evidences of an abnormal purine metabolism have been regarded as the most prominent feature of gout, modern writers more and more are coming to view the abnormalities of purine observed in gout as the result rather than the cause of the disease and as of secondary importance. Thus Knaggs,<sup>39</sup> after a study of the Strangeways collection

37 Richardson, Russell. Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, *J Clin Investigation* **13** 949 (Nov) 1934

38 Dr P. S. Hench supplied the material for this section.

39 Knaggs, R. L. A Report on the Strangeways Collection of Rheumatoid Joints in the Museum of the Royal College of Surgeons, *Brit J Surg* **20** 113 (July) 1932

of specimens of diseased joints, suggested that the deposition of urates in the joints is relatively unimportant and a minor effect of metabolic changes in which other toxic bodies are produced in addition to urates. Gout, according to Knaggs, is closely akin to the rheumatoid infections. In the Strangeways collection nearly every specimen presents hypertrophic bony phenomena which apparently are followed by degenerative changes similar to those seen in atrophic (rheumatoid) arthritis. The characteristic pathologic changes are illustrated in Knaggs' article by several excellent photomicrographs by Rodman. Watson<sup>40</sup> has accepted Llewellyn's idea that the cause of gout is cellular sensitization, in other words, an allergic phenomenon, the exciting factor being endogenous or exogenous proteins of pathologic and biochemical origin, the predisposing factor being heredity.

The uric acid content of the blood in diabetes has received relatively little attention. Yet Ricci<sup>41</sup> noted that when diabetic subjects fasted the uric acid content of the blood was high in those to whom insulin was not given and normal in those to whom insulin was given and that, furthermore, the elevation of the uric acid content of the blood following a meal high in purine was more prolonged in persons with diabetes than it was in normal controls. Bertram<sup>42</sup> found that the uric acid content of the blood is greatly elevated in the absence of an increase in nonprotein nitrogen in patients with diabetes in a stage preceding coma or in coma. Quick reported that aceto-acetic acid administered orally to normal persons determines the output of uric acid and concluded that the retention of uric acid in diabetes, as in fasting and after a meal high in fat, is to be explained by the action of organic acids. Lactic acid, when given orally or when produced by strenuous exercise, by chloroform poisoning or by an excess of sodium bicarbonate, and benzoic acid, phenylacetic acid and numerous other aromatic acids, decreases the excretion of uric acid, and Quick<sup>43</sup> proposed the theory that the excretion of uric acid requires an adequate supply of anti-ketogenic material. In harmony with these observations is the report of Lockie and Hubbard<sup>43</sup> that they were able to precipitate an attack of gout in predisposed subjects by feeding a diet high in fat and that they could cause an attack to subside by giving a diet rich in carbo-

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40 Watson, A. G. Common Maladies and Their Treatment. Gout, Prescriber **27** 203 (June) 1933.

41 Ricci, quoted by Quick, A. J. A New Concept of the Significance of Uric Acid in Clinical Medicine, *M. Clin. North America* **17** 1326 (March) 1934.

42 Bertram, quoted by Quick, A. J. A New Concept of the Significance of Uric Acid in Clinical Medicine, *M. Clin. North America* **17** 1326 (March) 1934.

43 Lockie, L. M., and Hubbard, R. S., in Hench, P. S. Proceedings of the First Annual Meeting of the American Association for the Study and Control of Rheumatic Diseases. Third Conference on Rheumatic Diseases, *J. A. M. A.* **103** 1883 (Dec 15) 1934.

hydrate The scarcity of gout among patients with diabetes, as noted by Joslin<sup>44</sup> and others, and the infrequency of attacks of arthritis in our experience with patients living on ketogenic diets are difficult to reconcile with these observations

Since the advent of the newer methods of treatment for pernicious anemia, the occasional precipitation of an attack of gout by the administration of liver extract and a preparation of desiccated hog stomach has been reported Sears<sup>45</sup> discussed (1) the observation by Riddle of an increase of the uric acid in the blood twenty-four hours after starting treatment with liver extract, (2) 2 cases of gout attributed by Spence to the excessive ingestion of liver, and (3) a case observed by himself, in which a typical first attack of gout occurred on the thirty-sixth day of treatment with a preparation of desiccated hog stomach

The classic treatment of gout by the restriction of purine, hot and cold applications, rest and preparations of colchicum and cinchophen continues unchallenged and has remained unchanged for years When one recalls that aside from the use of cinchophen, introduced in 1908, there has been no major change in the therapy of gout since the introduction of colchicum in the sixteenth century, Williams'<sup>46</sup> protest "gout the reproach of medicine" seems appropriate Modern investigations have in part explained the rationale but have not materially altered the ancient principles of diet in gout Watson, holding to the allergic theory, has searched for some type of food to which his gouty patients may be hypersensitive The injudicious use of cinchophen may occasionally be responsible for hepatitis, which may or may not have serious consequences<sup>47</sup> Watson stated that "iodine in the form of potassium iodide controls the gouty state quite as effectively as cinchophen and much more safely" Summing up the arguments for and against the administration of cinchophen, Hench<sup>49</sup> concluded that if other available analgesics are effective, cinchophen should be avoided,

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44 Joslin, E P Treatment of Diabetes Mellitus, ed 4, Philadelphia, Lea & Febiger, 1928, p 177

45 Sears, W G The Occurrence of Gout During the Treatment of Pernicious Anemia, *Lancet* **1** 24 (Jan 7) 1933

46 Williams, Rendell Gout The Reproach of Medicine, *M J & Rec* **135** 143 (Feb 3) 1932

47 Beaver, D C The Pathologic Anatomy of the Liver in Cases of Poisoning by Cinchophen, *Proc Staff Meet, Mayo Clinic* **7** 425 (July 20) 1932 Weir, J F, and Comfort, M W Toxic Cirrhosis Caused by Cinchophen, *Arch Int Med* **52** 685 (Nov) 1933

48 This footnote was deleted by the author

49 Hench, P S Derivatives of Cinchophen and Their Toxicity, *Proc Staff Meet, Mayo Clinic* **7** 427 (July 20) 1932, Derivatives of Cinchophen and Their Toxicity, *New England J Med* **207** 949 (Nov 24) 1932

but when other remedies are ineffective, a trial of cinchophen is justified. Statistical data lead one to the conclusion that the chances of fatal poisoning from cinchophen are in reality very slight, the fatality being estimated by the research department of a reputable manufacturing concern as about 1 in 600,000. It has seemed wise to us to follow Weintraub's advice regarding the use of alkalis in association with cinchophen to prevent a possible deposition of urates in acid urine and to discontinue the use of cinchophen if at any time evidences of toxicity present themselves.

## PROGRESS IN THE STUDY OF NUTRITION

The past few years have seen a tremendous transition in the field of nutrition. The discovery of the vitamins and of the necessity for certain minerals in food has revolutionized the knowledge of nutrition and has aroused the keen interest not only of the medical profession but also of the public. The new knowledge of vitamins has served as a background for recent trends in nutrition which have been well emphasized by McLester<sup>50</sup> in his statement that "the day was when, in order properly to nourish the sick person, the physician told him what he must not eat, now he is told what he must eat." In other words, the tendency has been to get away from the treatment of disease alone and to consider the general nutritive state of the patient. For many years the interest in nutrition was directed largely to a study of the chemical character, digestion and metabolism of the principal food factors. In more recent times studies of the vitamins and minerals have emphasized in particular the first of these features. As a result there has been a tendency on the part of physicians to forget a very important phase of nutrition, namely, alimentation. In a splendid discussion of problems of nutrition, Mendel<sup>51</sup> has called attention to the lamentable lack of knowledge of alimentation, especially of the mechanism of the absorption of foods.

## VITAMINS AND MINERALS

Interest in the vitamins in the past year has been directed particularly toward chemical identification of these essential food factors and their significance in resistance to infection. Because the discovery of the various vitamins came so rapidly and since the amounts essential for health were excessively small, chemical identification was delayed. The average person is likely to think of them as a group of substances perhaps related physiologically, if not chemically. However, added

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50 McLester, J. S. Changing Concepts of Nutrition, *J. A. M. A.* **103** 383 (Aug. 11) 1934.

51 Mendel, L. B. The Outlook in the Science of Nutrition, *Science* **78** 317 (Oct. 13) 1933.

knowledge continually emphasizes the chemical and physiologic differences of these substances. In one respect all known vitamins are similar in that man is dependent on exogenous sources for his supply of them.

*Vitamin A*—The relationship of certain natural pigments and vitamin A was early recognized and led subsequently to the demonstration by von Euler in Sweden and by Moore in England that very small doses of the yellow pigment carotene in purified form would cure rats exhibiting symptoms of the lack of vitamin A. Recently evidence has been presented which suggests a relationship between another pigment group, the flavines, and vitamin G. Studies of the chemical relation of carotene and vitamin A and of the nature of the vitamin have progressed to the stage which indicates that while alpha, beta and gamma carotene are sources of vitamin A, beta carotene is the best source. In fact, the recently adopted international standard for vitamin A is pure beta carotene, which has a melting point of 184 C (336.2 F) and which is optically inactive. Vitamin A is the primary alcoholic derivative produced by the symmetrical division into two parts of the beta carotene molecule, which has the chemical formula  $C_{40}H_{56}O$ . There has been great interest in recent years in the study of the occurrence of carotene in various foods and of metabolism and conversion to vitamin A in the animal organism. It has been demonstrated definitely that the carotene and the vitamin A content of various samples of the same type of food may differ considerably. In their studies of fresh fish oils Lovern, Edisbury and Morton<sup>52</sup> demonstrated that the oils vary in vitamin A content as much as 2,500 times. Halibut liver oil was found to be by far the richest known source of this vitamin, although the vitamin content of various oils of the halibut varied from 0.17 to 10 per cent, not only were there seasonal fluctuations, but in general the older and larger fish proved a better source of supply than the younger and smaller fish. Similarly, a study of the vitamin content of butter by Baumann and Steenbock<sup>53</sup> indicated that butter made in the summer contains a greater concentration of both carotene and vitamin A than that made in other seasons, there is a difference of 100 per cent between the vitamin A content of butter made in April and that of butter made in August. These workers demonstrated also that only 12 per cent of the total vitamin A potency of butter is accounted for by the carotene which is present. The balance is present as vitamin A.

52 Lovern, J. A., Edisbury, S. R., and Morton, R. A. Variations in Vitamin A Content of Fish-Liver Oils, with Particular Reference to Seasonal Fluctuations in the Potency of Halibut-Liver Oil, *Biochem J.* **27** 1461, 1933.

53 Baumann, C. A., and Steenbock, H. Fat-Soluble Vitamins. XXXVI. The Carotene and Vitamin A Content of Butter, *J. Biol. Chem.* **101** 547 (July) 1933.



The intestinal absorption of carotene and vitamin A has been demonstrated to constitute a variable factor in supply. In studies of this phase of metabolism, von Euler and Klusmann<sup>54</sup> demonstrated again the important rôle played by bile salts in absorption, for when dispersed in colloidal form in aqueous fluids carotene does not penetrate biologic membranes, but carotene and carotenoid pigments pass into aqueous solution in the presence of bile salts. It is supposed that following absorption carotene is again displaced from its association with bile salts. From the practical standpoint, Clausen<sup>55</sup> suggested that for rapid storage the feeding of vitamin A is superior to the administration of carotene because the former is more rapidly absorbed and in the presence of fever or diarrhea carotene is poorly absorbed. Similarly, Baumann, Rising and Steenbock<sup>56</sup> found a parallelism in the amount of vitamin A in the diet and that in the liver, even though only from 10 to 20 per cent of ingested vitamin is recovered from this organ. Apparently much of this vitamin is destroyed in the digestive tract.

The liver, recognized for years as the storehouse for vitamin A, is still considered to play an uncertain rôle in its metabolism. The results of earlier studies, which suggested the conversion of carotene to vitamin A by the action of hepatic enzymes have been questioned recently by Drummond and MacWalter,<sup>57</sup> who following the injection of carotene into the portal vein of rabbits found no increase in the amount of vitamin A in the liver for eight days. They were unable to obtain a conversion of carotene to vitamin A *in vitro* by incubation with liver tissue. Estimations of the vitamin A content of the liver at necropsy have been of interest but have not been illuminating. Muller and Suzman<sup>58</sup> in 106 cases observed at necropsy found a marked variation in the vitamin A content of the liver. In 11.3 per cent of the cases no vitamin A was found, and no relation could be established statistically between the cholesterol and the vitamin A content of the liver.

There is still almost complete ignorance of the facts concerning the mechanism of vitamin A activity. Carotene is almost always present in the blood of persons more than 2 years of age. The amount of carotene or of vitamin A in the blood is not an indication of the amount

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54 von Euler, Hans, and Klusmann, Erika. Zur Biochemie der carotinoide und des vitamins C (Ascorbinsäure), *Ztschr f physiol Chem* **219** 215, 1933.

55 Clausen, S. W. Limits of the Anti-Infective Value of Provitamin A (Carotene), *J A M A* **101** 1384 (Oct 28) 1933.

56 Baumann, C. A., Rising, B. M., and Steenbock, Harry. The Absorption and Storage of Vitamin A by the Rat, *J A M A* **103** 114 (July 14) 1934.

57 Drummond, J. C., and MacWalter, R. J. The Biological Relation Between Carotene and Vitamin A, *Biochem J* **27** 1342, 1933.

58 Muller, G. L., and Suzman, M. M. The Cholesterol and Vitamin A Content of the Liver in Man. A Study of One Hundred and Six Livers Obtained at Autopsy, *Arch Int Med* **54** 405 (Sept) 1934.

which may be stored in the liver. It may be said broadly that the essential function of vitamin A is to maintain the integrity and normal state of the epithelial structure of the animal organism. The close relation of vitamin A to the visual purple of the retina, to the maintenance of a normal epithelial barrier against infection and to growth is evidence of its versatility. As expressed by Orr and Richards,<sup>59</sup> the most important rôle of vitamin A in nutrition lies in its power to prevent the onset of pathologic conditions which are the cause of the loss of weight that occurs in deficiency of vitamin A.

It is almost uniformly understood that states of vitamin A deficiency are rare among civilized peoples. In the past year interesting contributions have been made which suggest that this is not strictly true. For example, Jeans and Zentmire,<sup>60</sup> in a study of sensitivity to light following partial adaptation to darkness of 213 children, found a group (about 20 per cent) with subnormal vision in the dark who were relieved promptly by the use of cod liver oil. They interpreted this as evidence of an abnormality previously unrecognized by the patients and the result of vitamin A deficiency. Further proof must be forthcoming before this important suggestion can be accepted as a fact.

Within the past year sufficient reports have accumulated from reliable sources to establish the occurrence of a distinct dermatologic lesion as the result of vitamin A deficiency. Loewenthal<sup>61</sup> in his study of conditions in East African prisons found that 74 of 81 prisoners had characteristic dermatitis and that 45 had xerophthalmia. Several authors have expressed the opinion that the cutaneous changes occur before either xerophthalmia or night blindness, the latter was previously thought to be the earliest symptom. The cutaneous changes consist of keratinization of a hard, dry, red papular type, resembling goose skin and most marked on the extensor surfaces.<sup>62</sup>

The relationship of vitamin A and infections, which still constitutes a problem requiring further study, will be considered subsequently.

*The Vitamin B Complex*—There is ample chemical and physiologic evidence to indicate that the original vitamin B discovered by Funk is in reality a complex and probably consists of several distinct chemical enti-

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59 Orr, J. B., and Richards, Marion B. Growth and Vitamin A Deficiency, *Biochem J* **28**:1259, 1934.

60 Jeans, P. C., and Zentmire, Zelma. A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J. A. M. A.* **102**:892 (March 24) 1934.

61 Loewenthal, L. J. A. A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, *Arch. Dermat. & Syph.* **28**:700 (Nov.) 1933.

62 Goodwin, G. P. A Cutaneous Manifestation of Vitamin A Deficiency, *Brit. M. J.* **2**:113 (July 21) 1934.

ties Already, the existence of vitamins  $B_1$ ,  $B_2$ ,  $B_3$ ,  $B_4$  and  $B_6$  have been described, although they are not universally accepted Vitamin  $B_2$  is recognized by many as vitamin G Studies of vitamin  $B_1$  in the past year have been limited largely to experimental work Clinical interest in this vitamin has not been as great as that in other vitamins because the outstanding clinical manifestation of its deficiency, beriberi, is unusual in this country However, recent studies by Cobb, Strauss and their associates<sup>63</sup> have suggested the importance of this vitamin in neurologic disturbances It seems a safe conclusion at present that the clinician need have little concern regarding a sufficiency of vitamin  $B_1$  in the diet of the average American Although vitamin  $B_1$  is apparently not stored in any quantity in the body, its supply is generally abundant and there is no evidence that maximal quantities are of greater value than a normal supply

The chemical identity of vitamin  $B_1$  is unknown, although active crystalline products have been produced It appears from the study of Birch and Harris<sup>64</sup> to have the property of a coenzyme-like substance intervening in the chain of reactions in the oxidation of carbohydrate Apparently it is particularly active in the chain involving the formation and oxidation of lactic acid Harris and Birch emphasized that vitamin  $B_1$  is not identical with the coenzyme of Benga and Szent-Gyorgyi for lactic acid dehydrogenase, although closely related to it In an attempt to determine the structure of vitamin  $B_1$ , Sure<sup>65</sup> found that pure irradiated adenine sulphate was a complete failure as a source of vitamin  $B_1$  for growth The bradycardia characteristic of beriberi and vitamin  $B_1$  deficiency, previously correlated with the accumulation of lactic acid, is corrected by the administration of vitamin  $B_1$  Another physiologic rôle is suggested by the experimental work of Cowgill and Gilman,<sup>66</sup> who concluded that so far as any diminution of the gastric secretion is concerned in animals lacking the vitamin B complex, this is due to absence of the  $B_1$  component That vitamin  $B_2$  (G) plays a significant rôle in this relationship is unlikely, but the point is not yet proved

The Second International Conference on Vitamin Standardization recommended the continuance of the previous standard In fact, the

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63 Minot, G R, Strauss, M G, and Cobb, Stanley "Alcoholic" Polyneuritis, Dietary Deficiency as a Factor in Its Production, *New England J Med* **208** 1244 (June 15) 1931

64 Birch, T W, and Harris, L J Bradycardia in the Vitamin  $B_1$  Deficient Rat and Its Use in Vitamin  $B_1$  Determinations, *Biochem J* **28** 602, 1934

65 Sure, Barnett Irradiated Adenine Sulphate as a Source of Vitamin B for Growth, *Biochem J* **27** 2043, 1933

66 Cowgill, G R, and Gilman, Alfred Physiology of the Vitamins XXIII The Effect of Lack of Vitamin B Complex on the Secretion of Gastric Juice in Dogs with Gastric Pouches, *Arch Int Med* **53** 58 (Jan) 1934

conference found the previous vitamin B<sub>1</sub> standard to be the most satisfactory that had been established. The standard, of which there is a supply sufficient for many years, is an adsorbate on acid clay.

There may be a need in the future for the parenteral use of vitamins, although the need will likely always be considerably restricted. The recent efforts of Stuart, Block and Cowgill<sup>67</sup> to prepare an inexpensive and easily prepared solution of vitamin B<sub>1</sub> which would be suitable for parenteral use have been successful.

There has been much debate on the significance, so far as deficiency disease is concerned, of atrophy of the mucous membranes of the tongue. Steenbock and his associates<sup>68</sup> presented evidence which they believed showed that atrophic glossitis in the rat and in man is dependent on a deficiency of vitamin B<sub>1</sub>. The clinical evidence of this fact is not completely convincing.

*Vitamin B<sub>2</sub>*—In the mind of some investigators the so-called vitamin B<sub>2</sub> is nothing more than an abundant supply of vitamin B<sub>1</sub>. So far as is known, there is no clinical application of this knowledge.

O'Brien<sup>69</sup> has evidence which he believes justifies the opinion that vitamin B<sub>2</sub> is distinct from vitamin B<sub>1</sub>, in fact, some features suggest that it is an amino-acid. That the whole of the vitamin B complex does not consist of vitamins B<sub>1</sub> and B<sub>2</sub> (G) was strongly suggested by Booher, Blodgett and Page,<sup>70</sup> who found that a vitamin G concentrate with a vitamin B<sub>1</sub> crystalline product did not constitute the vitamin B complex.

*Vitamin C*—Recent studies which have elucidated the chemical nature of vitamin C have added another brilliant chapter to the history of scurvy. To Szent-Gyorgyi<sup>71</sup> and King<sup>72</sup> and their associates must go the credit for independently establishing the fact that vitamin C is cevitamic acid (introduced as ascorbic acid). The chemical formula of cevitamic acid (first called hexuronic acid) is C<sub>6</sub>H<sub>8</sub>O<sub>6</sub>. Its powerful capacity as a reducing agent is well recognized, but the exact mechanism of its physiologic action is still not clear. There is debate as to

67 Stuart, E. H., Block, R. J., and Cowgill, G. R. The Antineuritic Vitamin V. The Preparation of a Vitamin Concentrate Suitable for Parenteral Use, *J. Biol. Chem.* **105** 463 (June) 1934.

68 Hutter, A. M., Middleton, W. S., and Steenbock, Harry. Vitamin B Deficiency and the Atrophic Tongue, *J. A. M. A.* **101** 1305 (Oct. 21) 1933.

69 O'Brien, J. R. Vitamin B<sub>2</sub>, *Biochem. J.* **28** 926, 1934.

70 Booher, Lela E., Blodgett, H. M., and Page, J. W. Investigations of the Growth-Promoting Properties of Vitamin G Concentrates, *J. Biol. Chem.* **107** 599 (Nov.) 1934.

71 Svirbely, S. L. and Szent-Gyorgyi, Albert. The Chemical Nature of Vitamin C, *Biochem. J.* **26** 865, 1932.

72 Waugh, W. A., and King, C. G. Isolation and Identification of Vitamin C, *J. Biol. Chem.* **97** 325 (July) 1934.

the relation of cevitamic acid to the endocrine glands, particularly to the suprarenals. The most obvious effects of its absence are on the capillaries and perhaps also on the teeth. The loss of normal features by the intercellular capillary substance leads to hemorrhages which are characteristic of scurvy. Other physiologic functions of cevitamic acid, which have been suggested by Harris and Ray,<sup>73</sup> are the maintenance of the functional activity of certain types of cells (osteoblasts, odontoblasts, cementoblasts), and the prevention of their premature degeneration. There is, however, no appreciable local concentration of cevitamic acid in the teeth and in the bones. Presnell<sup>74</sup> added evidence which indicates that in the experimental animal receiving insufficient quantities of vitamin C, the number of blood platelets decreases and anemia occurs, this suggests that the bleeding in scurvy may be caused not only by changes in the vascular system but by alterations in the blood.

In keeping with the recognition that cevitamic acid is vitamin C, the newly adopted international standard for this substance is l-cevitamic acid, as defined by certain physical constants.

Other significant achievements in the chemistry of vitamin C have been the development of an indirect chemical method for the estimation of cevitamic acid by Harris and Ray and the synthesis of cevitamic acid in the laboratory. The former discovery has permitted studies not only of the cevitamic acid content of foods but also of some of the metabolic features of vitamin C. The quantity of cevitamic acid in the juice of various citrous fruits, particularly in lemon juice, previously was thought to be constant. In fact, the first international unit consisted of a certain quantity of lemon juice. However, Bacharach, Cook and Smith,<sup>75</sup> in their studies of the cevitamic acid content of citrous fruits, found variability even in fruit from the same consignment. Oranges contained a mean value of 51 mg per hundred cubic centimeters, tangerines, 37 mg, and lemons, 64 mg. The storage of fruit for one month caused a loss of only 6 per cent of the cevitamic acid content of lemon juice.

It was estimated by Harris, Ray and Ward<sup>76</sup> that the minimal daily requirement of cevitamic acid is that contained in 30 cc of orange

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73 Harris, L. J., and Ray, S. N. Standardization of the Anti-Scorbutic Potency of Ascorbic Acid, *Biochem J* **27** 2016, 1933.

74 Presnell, A. K. The Relation of Avitaminosis C to Blood, *J Nutrition* **8** 69 (July) 1934.

75 Bacharach, A. L., Cook, Phyllis M., and Smith, E. L. The Ascorbic Acid Content of Certain Citrous Fruits and Some Manufactured Citrous Products, *Biochem J* **28** 1038, 1934.

76 Harris, L. J., Ray, S. N., and Ward, Alfred. The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, *Biochem J* **27** 2011, 1933.

juice, or about 20 mg. It has been recognized for years that vitamin C is not stored in the body in any great quantity. However, as was demonstrated by Szent-Gyorgyi,<sup>77</sup> the suprarenal glands contain appreciable quantities of vitamin C. Harris and Ray<sup>78</sup> examined the suprarenal glands of the ox and found that the cevitamic acid content of the medulla is two-thirds that of the cortex and that both are rich in cevitamic acid. In fact, both contain more than orange juice contains, weight for weight. There has been much discussion of the relationship of cevitamic acid and the suprarenal hormone. Grollman and Firor<sup>79</sup> studied the problem and produced evidence which suggests that the apparent intimate relation between the suprarenal cortex and the deficiency of vitamins is explainable on the assumption that the hormones and vitamins are necessary for the proper functioning of a great number of organs and tissues. They expressed the belief that the apparent partial replaceability of vitamin C by preparations of the suprarenal cortex is the result of the presence of cevitamic acid in such extracts. On the other hand, cevitamic acid does not prolong the life of suprarenalectomized animals.

In experimental scurvy in guinea-pigs Siehrs and Miller<sup>80</sup> have found that cevitamic acid in the cortex of the suprarenal glands disappears progressively during the progress of the disease. In fact, the staining reaction to silver nitrate indicates a decrease in the cevitamic acid content after the animal has been on a scorbutic diet for one day, and a minimum amount of staining occurs on the sixth day. When 3 cc. of orange juice is fed there is a prompt reappearance of acid in the cortex of the suprarenal glands.

Under ordinary conditions cevitamic acid is excreted in the urine in approximately uniform quantities. This amounts to about 30 mg. daily, according to Harris, Ray and Ward. The importance of this observation cannot yet be estimated. It is possible that a measurement of the amount of cevitamic acid in the urine will prove of value clinically. In studies of the effect of the ingestion of large quantities of cevitamic acid on urinary excretion, Harris, Ray and Ward demonstrated that if 600 cc. of orange juice was given, the concentration of cevitamic acid in the urine rose sharply to from eight to ten times the normal

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77 Szent-Gyorgyi, Albert. Observations on the Function of Peroxidase Systems and the Chemistry of the Adrenal Cortex, *Biochem J* **22** 1387, 1928.

78 Harris, L. J., and Ray, S. N. Vitamin C in the Suprarenal Medulla, *Biochem J* **27** 2006, 1933.

79 Grollman, Arthur, and Firor, W. M. Studies of the Adrenal. VII. The Relation of the Adrenal Cortical Hormone to the Vitamins, *J. Nutrition* **8** 569 (Nov. 10) 1934.

80 Siehrs, A. E., and Miller, C. O. Disappearance of Vitamin C from the Adrenals of Scorbutic Guinea Pigs, *J. Nutrition* **8** 221 (Aug. 10) 1934.

amount and then rapidly dropped to normal within one day. The normal daily loss of from 30 to 33 mg is maintained even though the subject remains on a diet free from vitamin C for one week. This amount incidentally, is greater than the daily requirement of cevitamic acid for man, however, the average person consumes more than his actual requirement. Johnson and Zilva<sup>81</sup> suggested some variability in the urinary excretion of cevitamic acid, depending on the amount stored in the body and on the quantity consumed in the food. They discovered that with a complete store in the body a more or less constant level of excretion is maintained.

Parenteral injections of preparations of vitamin C have been used for several years. Dry<sup>82</sup> mentioned the intravenous use of buffered orange juice in cases of scurvy. Bauke,<sup>83</sup> by giving 100 mg of l-cevitamic acid intravenously each day to a patient who had scurvy, recently obtained good results and an apparent reduction in the period of recovery.

There has been much discussion of the value of tests of capillary resistance in the diagnosis of latent scurvy. Schultzer<sup>84</sup> and Dalldorf,<sup>85</sup> who have faith in such tests, found latent scurvy to be not uncommon among hospital patients and children from poor homes. However, others have insisted that decreased capillary resistance is not sufficient evidence of deficiency of vitamin C. It seems reasonable to place the burden of proof on those who accept the test. It is difficult to believe that latent scurvy is as common as some of the studies indicate.

The relation of vitamin C to dental caries is still a subject of such wide debate and uncertainty that it will not be considered at this time.

*Vitamin D*—Recent interest in vitamin D has been concerned chiefly with (1) the daily requirement of adults and children, (2) the most satisfactory form in which it may be administered and (3) its significance in rickets and dental caries.

It is widely accepted that vitamin D is viosterol (irradiated ergosterol), probably one of the many possible stereo-isomers of ergosterol. There is still evidence which tends to prevent the universal acceptance

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81 Johnson, S. W., and Zilva, S. S. The Urinary Secretion of the Ascorbic and Dehydroascorbic Acids in Man, *Biochem J* **28** 1393, 1934.

82 Dry, T. J. Avitaminosis in Natives of Rhodesia, *Arch Int Med* **51** 679 (May) 1933.

83 Bauke, E. E. Parenterale C—Vitamin—(Cebion—) Behandlung bei Skorbut, *Munchen med Wchnschr* **81** 1240 (Aug 10) 1934, abstr, *J A M A* **103** 1187 (Oct 13) 1934.

84 Schultzer, P. Studies on Capillary Resistance. I. Lowered Resistance Due to Vitamin C Deficiency and Other Conditions in Hospitalized Patients, *Acta med Scandinav* **81** 113, 1934.

85 Dalldorf, G. Sensitive Test for Subclinical Scurvy in Man, *Am J Dis Child* **46** 794 (Oct) 1933.

of viosterol as the only antirachitic factor despite its preparation in crystalline form Kon and Booth<sup>86</sup> suggested, for example, a true chemical difference between the antirachitic factor of butter and the antirachitic factors of cod liver oil and viosterol

The international unit for vitamin D has remained unchanged, consisting of viosterol in olive oil

One difficulty which has arisen in experimental work on vitamin D is that animals do not utilize different antirachitic materials in the same proportion This variation in the utilization of antirachitic material by the same or different organisms is still unexplained Friedman,<sup>87</sup> after an extensive review of the literature, pointed out, for example, that there is extensive clinical evidence to the effect that far fewer units of vitamin D in the form of milk containing vitamin D are required to protect against, or to heal, rickets than are required with other antirachitic agents His studies suggest that of the various methods of augmenting the vitamin D content of milk, the most satisfactory are the direct irradiation of the milk and the direct addition of vitamin D concentrates to milk

Despite the fact that information is now at hand which should permit the prevention and healing of rickets, the disease is still prevalent Harris<sup>88</sup> noted that recent official reports disclose that no less than from 80 to 90 per cent of the elementary school population in London shows evidence of some degree of rickets There is discussion as to the most satisfactory method of preventing and of healing rickets and as to the relationship of the optimal and toxic doses of the various antirachitic agents Irradiated yeast, viosterol, cod liver oil and milk which has been augmented with vitamin D are advocated The very important question of the advisability or practicability of augmenting all milk with vitamin D has been raised The answers to all of these questions are not ready Further experimental work and clinical observation will be necessary before it can be stated definitely what is the optimal requirement for each of the various antirachitic preparations

The mechanism of action of vitamin D in the normal mineralization of bone and in the prevention and healing of rickets is not clear The suggestion is made that vitamin D not only increases the absorption of calcium and of phosphorus but acts in other phases of the metabolism of bone

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86 Kon, S K and Booth, R G The Vitamin D Activity of Butter I A Chemical Differentiation of the Antirachitic Factor of Autumn and Winter Butter from Irradiated Ergosterol and Vitamin D of Cod Liver Oil, *Biochem J* **27**, 1302, 1933

87 Friedman, Samuel Vitamin D Milk A Résumé, *J Pediat* **4** 678 (May) 1934

88 Harris, L J The Significance of Vitamins in Practical Experience, *Brit M J* **2** 367 (Aug 26) 1933



Another interesting aspect of the metabolism of vitamin D is suggested by the studies of Light, Wilson and Frey,<sup>89</sup> who found that when vitamin D is supplied as irradiated yeast in the diet of the cow it is practically completely absorbed, that it disappears rapidly from the blood at a maximal rate of 10 per cent per hour and nevertheless that only from 2 to 3 per cent appears in the milk. The place and manner of destruction of the remainder are unknown. A slight amount of it is reexcreted into the intestine.

The significance of vitamin D in dental caries is such a disputed problem that it will not be considered here.

*Vitamin G (B<sub>2</sub>)*—Recent interest in vitamin G has centered about its significance as a hematopoietic substance and about its relation to pellagra. The brilliant work of Castle,<sup>90</sup> which has been confirmed by others, at first suggested that vitamin G might be the extrinsic factor which when combined with an intrinsic factor supplied normally by the gastric mucosa forms an active and normal hematopoietic agent. The evidence of this relationship is not well established, and the recent work of Wills<sup>91</sup> and of the Lassens<sup>92</sup> suggests that the extrinsic factor is not vitamin G, because normal gastric juice incubated with purified sources of vitamin G was discovered to be ineffective in producing a remission when fed to patients who had pernicious anemia.

Conservative clinicians have remained somewhat skeptical about accepting the evidence that a deficiency of vitamin G is entirely responsible for pellagra, despite the splendid early work of Goldberger and his associates. In the past year further evidence of an unknown factor in the production of pellagra has been advanced. McLester<sup>93</sup> called attention to the apparent impossibility of invariably relating pellagra to faulty diet, to the failure in many cases to correct this disorder by dietary means and to the epidemiologic characteristics of the disease. He expressed the belief that the most likely etiologic factors, in the order of prominence, are multiple food deficiency and, directly or indirectly, infective agents. It seems reasonable to agree with McLester that, despite the careful work that has been done, the last word regarding the nature of pellagra is yet to be said.

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89 Light, R. F., Wilson, L. T., and Frey, C. N. Vitamin D in the Blood and Milk of Cows Fed Irradiated Yeast, *J. Nutrition* **8** 105 (July) 1934.

90 Castle, W. B., and Locke, E. A. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *J. Clin. Investigation* **6** 2 (Aug) 1928.

91 Wills, Lucy. The Nature of the Haemopoietic Factor in Marmite, *Lancet* **1** 1283 (June 17) 1933.

92 Lassen, C. A., and Lassen, H. K. Yeast or Vitamin B<sub>2</sub> as "Extrinsic Factor" in Treatment of Pernicious Anemia, *Am. J. M. Sc.* **188** 461 (Oct) 1934.

93 McLester, J. S. The Nature of Pellagra. A Critique, *Ann. Int. Med.* **8** 475 (Oct) 1934.

The chemical nature of vitamin G is not certain. A relationship to the pigment group of the flavines is apparent. At the Second International Conference on Vitamin Standardization the establishment of pure lactoflavine as a standard for vitamin B<sub>2</sub> (G) was considered, but its use was held to be premature. One reason for this attitude was that a deficiency of vitamin G is not definitely connected with any disease or syndrome which affects man. This is a rather remarkable conclusion when one takes into consideration that, in America at least, it is widely recognized and accepted by many that a deficiency of vitamin G leads to the development of pellagra. However, the conclusion of the conference, which was formed by a distinguished group of scientists, was unanimous.

If the results in animals obtained by Sherman and Ellis<sup>94</sup> with vitamin G can be confirmed in man, one of the most interesting and important developments in the knowledge of nutrition lies ahead. These investigators have been feeding rats with amounts of vitamin G at four different levels. The young of rats with the highest intake of vitamin G showed a superior vitality and a prolongation of the period between the attainment of maturity and the onset of senility. These experiments reaffirm previous work by Sherman and make clear that the optimal intake of vitamin G is much more than the amount demonstrated as strictly necessary. It seems reasonable to speculate that this may be true also of some of the other essential food factors.

*Vitamin E*—While vitamin E is recognized as being essential for certain experimental animals, there is still no evidence that it has any clinical significance in man.

*Excessive Dosage of Vitamins and of Foods Containing Them*—While the qualitative aspects of vitamins as essential food factors are well recognized, there is a paucity of information with regard to the quantitative requirements. This has led to much confusion, which has been increased by the lack of information concerning the chemistry, absorption and metabolism of the vitamins. Consequently it has been impossible to establish levels of minimal requirement, and there has been speculation as to the optimal requirement and as to whether larger than optimal quantities of a vitamin will lead to improvement in health and greater resistance to infection. It has been suggested that this is true in the case of vitamins A and G. With the preparation of vitamins in concentrated and crystalline form and because the vitamins normally seem to be required only in minute amounts, the problem has arisen of the possibility of toxic effects from excessive doses. On this point there are several interesting observations.

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<sup>94</sup> Sherman, H. C., and Ellis, L. N. Necessary Versus Optimal Intake of Vitamin G (B<sub>2</sub>), *J. Biol. Chem.* **104**: 91 (Jan.) 1934.

Considerable interest has been aroused in the toxicity of excessive doses of cod liver oil. It is true, as Cox and Roos<sup>95</sup> pointed out, that the toxicity of cod liver oil must be considered separately from hypervitaminosis D, since the dosage of cod liver oil necessary to induce pathologic calcification would have to be calculated in liters. Andersson,<sup>96</sup> experimenting with white mice and using daily doses of 3 cc of cod liver oil per kilogram of body weight, found pathologic changes characterized by pigmentary and vacuole degeneration of muscle, transformation of the muscle cells into connective tissue and sometimes fatty infiltration and calcareous and waxy degeneration of the muscles. Apparently complete restitution to normal never occurred after the cessation of the administration of cod liver oil. Cox and Roos could demonstrate no histologic lesions in the hearts of rats which for one hundred and thirty days had been fed a diet which was adequate in protein, salts and vitamins and contained 78 per cent of calories as cod liver oil, but the rate of growth was definitely subnormal. The amount of cod liver oil administered in these experiments was 27.3 Gm. for each kilogram of body weight. In an attempt to explain abnormal changes after the administration of cod liver oil, such as those reported by Agduhr, Cox and Roos suggested that the toxic effects noted by others after the use of doses one-sixtieth as large as theirs may have been the result of a faulty interpretation of the histologic sections, of a deficiency of some accessory food constituents or of the presence of toxic substances in the oil.

The toxic effect of excessive quantities of viosterol possibly may be explained by the presence of toxic products. This may explain such toxic manifestations as have followed the administration of relatively low doses of viosterol, although Drummond<sup>97</sup> stated that it has been finally proved that the toxicity may be the result of exaggerated action of the vitamin as well as the result of toxic contaminants. Hauch<sup>98</sup> noted that, in general, the more complete and better balanced a diet is, the more protection it gives against the toxicity of excessive amounts of vitamin D.

In a discussion of the symptoms of overdosage of viosterol in his studies of 300 subjects, Reed<sup>99</sup> pointed out that toxicity in many cases

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95 Cox, W. M., and Roos, A. J. On the Alleged Toxicity of Cod Liver Oil, *Bull. Johns Hopkins Hosp.* **44** 430 (June) 1934.

96 Andersson, Hjalmar. Concerning Some Cod Liver Oil Lesions and Their Healing Tendency. *Uppsala Lakareforh.* **39** 27 (Dec.) 1933, abstr., *J. A. M. A.* **102** 810 (March 10) 1934.

97 Drummond, J. C. *Biochemical Studies of Nutritional Problems*, Lane Medical Lectures, Stanford University, Calif., Stanford University Press, 1934.

98 Hauch, J. T. Studies on the Effect of High Doses of Irradiated and Non-Irradiated Ergosterol on the Albino Rat, *J. Nutrition* **8** 163 (Aug. 10) 1934.

99 Reed, C. T. Symptoms of Viosterol Overdosage in Human Subjects, *J. A. M. A.* **102** 1745 (May 26) 1934.

may be recognized very early by the subjects themselves and before any serious damage has occurred. An increased frequency of urination is the most common initial symptom. Anorexia and nausea also occur, acute gastro-intestinal symptoms appear later, but there is no fever. Muscular weakness, lassitude, dull aching in the muscles, dizziness and disturbed muscular coordination and equilibrium may develop. It appears from these studies that there need be no apprehension about the administration of amounts ranging up to 150,000 international units daily for an indefinite period (the normal antirachitic dose is 3,000 international units). In contrast to this, Harris stated that the minimal toxic dose is 10,000 international units daily. This investigator, who has expressed the belief that viosterol is the best antirachitic agent in the treatment of rickets, has suggested that the toxic dose is close to the optimal daily therapeutic dose of from 3,000 to 5,000 units.

In their studies of the effect of large doses of vitamin A, Davis and Moore<sup>100</sup> reported that with large, nontoxic doses the amount in the liver was very high. The lungs and kidneys also held some vitamin A, but other organs contained very little, with the exception of the suprarenal glands. With massive doses of vitamin A in young rats there developed emaciation, hemorrhagic retinitis and a loss of hair about the mouth. Hypervitaminosis A could not be produced by feeding carotene because carotene is of limited solubility and therefore of limited dosage.

Toxic manifestations from excessive quantities of vitamin A have not been reported in man. Similarly, the effect of excessive doses of vitamin B is unknown. Demole<sup>101</sup> could find no evidence experimentally of hypervitaminosis C. In dogs receiving l-cevitic acid in large doses there developed no symptoms or histologic changes. Excessive quantities of cevitic acid are rapidly excreted in the urine.

In summarizing the evidence it seems fair to state that with the exception of the established toxicity of very large doses of viosterol or of smaller doses of improperly irradiated ergosterol there need be little concern at present on the score of overdosage of the vitamins.

*Iron and Copper*—There has been much clinical interest in recent years in the relationship of iron and copper to the formation of hemoglobin. The work of Whipple in studying the effect of various foods on the regeneration of hemoglobin in dogs in which the hemoglobin reserves had been depleted by repeated bleeding served as the initial

100 Davis, A. W., and Moore, Thomas. Vitamin A and Carotene. XI. The Distribution of Vitamin A in the Organs of the Normal and Hypervitaminotic Rat, *Biochem J* **28** 288, 1934.

101 Demole, Victor. On the Physiological Action of Ascorbic Acid and Some Related Compounds, *Biochem J* **28** 770, 1934.

stimulus Additional stimulus has been afforded by Mackay's recognition of the frequency of anemia in infancy and by the proof offered by her that the principal factor in the production of this anemia is a dietary deficiency Much useful information will be found in the splendid review of Davidson and Leitch<sup>102</sup> of the nutritional anemia which affects man and animals Some of the significant points are the following A deficiency in the diet of any element essential for the formation of erythrocytes, namely, constituents of the organic matrix or stroma, pyrrol either as protoporphyrine or in some simpler form, iron and the constituent amino-acids of globin, can lead to the development of anemia Extensive studies reveal a wide range of the iron content of milk Not only may there be a variation in the iron content of various foods but it must be recalled that although an adequate quantity is present in food, this does not necessarily indicate a high content of iron in a form which is capable of absorption The old idea of Bunge that only organic iron is absorbed has been replaced through demonstrations that iron to be absorbed must be soluble, ionizable and ultrafiltrable The iron of food is apparently wholly or chiefly ferric iron, and its availability depends largely on the presence of acid in the stomach, which plays a rôle in the production of ferrous iron, the form in which iron is apparently absorbed Davidson and Leitch pointed out that in achlorhydria there may be difficulty in liberating iron in food from the complexes in which it occurs and in reducing it to ferrous iron

Studies of the requirements and storage of iron give variable results While Sherman has suggested a standard of 15 mg per day, Davidson and his associates have demonstrated that health may be maintained in children and in adult men, but not always in women, on as little as 6 mg per day While evidence indicates that the amount of iron in the liver is easily increased by feeding iron and that it is regulated also by the rate of the destruction of erythrocytes, the amount of iron in the spleen and kidneys appears to depend chiefly on the latter factor An important factor, not itself a constituent of the hemoglobin molecule, affecting the utilization of iron and the formation of hemoglobin is copper Copper is contained in particular in liver, oysters, chocolate, cocoa and molasses

From the standpoint of considering anemia as a disease of nutritional deficiency it is necessary to describe one group as "direct," or the result of an actual quantitative insufficiency of the factors necessary for the formation of blood, and another group as "indirect," or the result of a failure of absorption from the intestinal tract In the prevention and treatment of nutritional anemia of adolescence, Davidson and Leitch suggested a daily supply of from 15 to 20 mg of iron, a quantity easily

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102 Davidson, L S P, and Leitch, I The Nutritional Anaemias of Man and Animals Nutrition Abstr & Rev 3 901 (April) 1934

obtained if reasonable care is paid to the ingestion of foods rich in iron. Women, who commonly have anemia, present a more difficult problem because of the simultaneous occurrence, frequently, of other etiologic factors. Iron and ammonium citrate in a dose of 30 grains (1.95 Gm.) three times a day, pills of ferrous carbonate, U. S. P., in a dose of 15 grains (0.97 Gm.) three times a day, reduced iron in a dose of 10 grains (0.64 Gm.) three times a day and ferrous sulphate, ferrous carbonate or ferrous chloride in a dose of 3 grains (0.19 Gm.), three times a day are equally efficacious in treatment. Evidence is steadily accumulating to show that the efficacy of a preparation of iron depends largely on the number of ferrous ions which are liberated in the small intestine. The advantages of adding copper in the treatment of nutritional anemia remain questionable. The amount of copper required is very small and is supplied by the copper which exists as an impurity in the preparations of iron dispensed for therapeutic purposes.

More information with regard to the requirement of iron and copper of growing children has been obtained from studies of the retention of iron and copper by Daniels and Wright<sup>103</sup>. They found the intake of iron of eight normal children from 4 to 6 years of age to range from 0.57 to 0.75 mg. for each kilogram of body weight, from 94 to 97 per cent of the excreted iron appearing in the feces. The daily intake of copper amounted to from 0.069 to 0.113 mg. for each kilogram of body weight. The excreted copper appeared largely in the feces. Undernourished children retained larger quantities of these essential elements than did children who were well nourished. The larger retention of copper, in general, occurred when the diet contained a larger quantity of this element. However, the amount of copper retained bore no constant relationship to the amount of iron retained.

#### RELATION OF THE NUTRITIVE STATE TO INFECTION

It is logical to suppose that there is a close relationship between the state of nutrition and the resistance to infection. It would be anticipated that the undernourished person would be more susceptible to the development of an infectious disease than the well nourished person. When one looks for evidence to substantiate this impression the search is not too fruitful. Interest in this subject was precipitated by the observation that animals which had been deprived of vitamin A were subject to infections, particularly of the eye. The public now is being bombarded with advertising of the "anti-infective" power of foods or drugs containing this or that vitamin, such as is found in the cough drops of the well known brotheis "Tyade" and "Mark."

103 Daniels, Amy L., and Wright, Olive E. Iron and Copper Retentions in Young Children, *J. Nutrition* 8:125 (Aug.) 1934.

The most important practical problem is not so much whether a person receiving an inadequate diet is less capable of resisting infection than is a normal person, but whether the amount of vitamin in excess of that normally obtained by well nourished persons will further increase the resistance to infection. In the past year there have appeared two extensive reviews on this subject. While the approach has been somewhat different in each case, the conclusions are much the same. The possibility that the diet may have some influence on the incidence, the course and the final outcome of infection is a comparatively recent idea. Among some of the difficulties raised by such a problem are the inability to subject patients to a controlled nutritional program, the ignorance of quantitative requirements of the vitamins and the lack, until recently, of pure preparations of the vitamins for experimental purposes. Consequently much that has been written on this subject is based on experiments on animals and on observations on relatively small groups of persons. Clausen<sup>104</sup> in his review came to the general conclusion that the susceptibility to infection is not, as a rule, affected by the diet but that resistance to infection, on the other hand, may be greatly diminished by a deficient diet. He said "A deficiency in the diet of vitamins A and C appears quite definitely to lower resistance to infection. In certain cases, a lack of the vitamin B complex may also do the same thing. A lack of vitamin D cannot be said to have a proven effect in lowering resistance. It seems probable that the existence of a partial deficiency of vitamins may result in loss of resistance to infection, though this cannot be said, from the present evidence to have been clearly established."

Resistance to infection is accomplished by different protective and immunologic factors and reactions. Consequently, a study of the effect of the vitamin content of the diet on the resistance to infection must take these several factors into consideration. Robertson<sup>105</sup> in her review has considered the available evidence with four criteria in mind: (1) a determination of any change in the natural immune bodies and in the cellular reactions which are the result of deficiency, (2) the assay of responses of the antibodies after the injection of appropriate antigens into experimental animals, (3) the relative liability to spontaneous infection after the defective feeding of animals, and (4) the comparative susceptibility to induced infections of persons who receive inadequate and those who have adequate diets. The conclusion is that although vitamin A is called the anti-infective vitamin little actual evidence exists with regard to this phase of its activity. The opinion

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104 Clausen, S. W. The Influence of Nutrition on Resistance to Infection, *Physiol Rev* **14** 309 (July) 1934

105 Robertson, E. C. The Vitamins and Resistance to Infection, *Medicine* **13** 123 (May) 1934

is expressed that beneficial effects follow its administration only when a patient has been subsisting on a diet that is partially deficient in vitamin A. Immunologic evidence is presented to show that neither scurvy nor a deficiency in vitamin B is attended by a consistent variation in the resistance to infection. On the whole, the effects of vitamin D in infection, which have been noted by many workers, have been variable, and it is impossible to draw satisfactory conclusions at present.

Several studies which have been reported since the reviews of Clausen and Robertson deserve attention. Beard,<sup>106</sup> for example, studied a group of 36 medical students, to each of whom were administered nine tablets daily for one year of a proprietary preparation of cod liver oil concentrate which contained vitamins A and D. In this group there was a reduction of 50 per cent in the incidence of colds, and 68 per cent of the infections which occurred were mild. On the other hand, there was no difference between the controls and those who took the concentrates so far as the incidence of influenza during an epidemic was concerned. Similarly, the Gardners<sup>107</sup> thought that supplementing the diet of school children with halibut liver oil or with foods particularly rich in vitamin A decreased the incidence of colds and produced a higher degree of general health, as shown by a greater gain in weight. Mackay<sup>108</sup> compared young children in London who received supplementary vitamin A with children who depended on dried milk until 8 months of age and thereafter on dried milk and ordinary table food for their supply of vitamin A. The incidence of minor "infective" lesions of the skin (sore buttocks, intertrigo and so forth) in the children who received added vitamin A was apparently only half that in the control group. There was no difference between the groups in growth, in the rate of gain in weight, in the incidence of respiratory or digestive diseases or in the number of infections. The significance of these findings is debatable, as Mackay pointed out, and may be representative of the fact that vitamin A deficiency is a common occurrence in infants who are artificially fed.

It is obvious from the conflicting character of the data that much more information is needed before the question at issue can be answered. The present position is well stated in an editorial<sup>109</sup> in *The Journal of*

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106 Beard, H. H. The Prophylactic Effect of Vitamin A and D upon the Prevention of the Common Cold and Influenza, *J. Am. Diet. A.* **10** 193 (Sept) 1934.

107 Gardner, Esther L., and Gardner, F. W. Vitamin A and Colds, *Am. J. Dis. Child.* **47** 1261 (June) 1934.

108 Mackay, Helen M. M. Vitamin A Deficiency in Children. II. Vitamin A Requirements of Babies, Skin Lesions and Vitamin A Deficiency, *Arch. Dis. Childhood* **9** 133 (June) 1934.

109 Nutrition and Resistance to Infection, editorial, *J. A. M. A.* **103** 994 (Sept. 29) 1934.



*the American Medical Association* "Despite the many demonstrated correlations between lack of an essential dietary factor and functional and structural change in the organism, there is surprisingly little cogent evidence of a specific relation between these factors and infection"

#### SIGNIFICANCE OF THE GASTRO-INTESTINAL TRACT IN NUTRITIONAL STATES

Bacteriologic and chemical studies created an erroneous conception of the nature of many diseases, since they gave rise to the thought that disease is always the result of the presence of some abnormal factor or positive agent in the living organism. This thesis became so firmly established that the opposite conception, namely, that the absence of a factor necessary for normal health can produce disease, was overlooked until the vitamins were discovered. And until recently too much emphasis probably was placed on the conception that diseases of dietary deficiency arise solely from a lack in the diet of a sufficient quantity of certain essential food factors. This undoubtedly is the most common cause of clinical and experimental states of deficiency, but it must be emphasized that deficiency may also result from a failure of adequate absorption or utilization of essential food factors. This last conception, which Strauss<sup>110</sup> said originated with Fenwick in 1880, has been developed only in the past few years. It seems reasonable to believe that in this country a large proportion of deficiency states arise from this cause, because the diet of the average American is probably adequate in its qualitative and quantitative aspects. The conception of the rôle of the gastro-intestinal tract in deficiency diseases, in brief, is that a deficiency disease in man may and frequently does develop in spite of an apparently adequate diet because of some disturbance of the gastro-intestinal tract. Attention has already been called to the lamentable lack of information with regard to alimentation. As Mendel has emphasized, there is a paucity of new or novel information about alimentation as well as a need of additional facts secured through new methods of attack on the problem of alimentation and absorption.

Among diseases which have been classified as belonging to the group which result from disturbances in gastro-intestinal function are pernicious anemia, pellagra, the polyneuritis of alcoholism and that of pregnancy, idiopathic hypochromic anemia, and the toxemia associated with intestinal obstruction and vomiting of pregnancy. Similarly, instances of night blindness, beriberi, pellagra, and nutritional edema have been described as a result of gastro-intestinal lesions which pre-

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110 Strauss, M. B. The Role of the Gastro-Intestinal Tract in Conditioning Deficiency Disease. The Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and Other Forms of Polyneuritis, *J. A. M. A.* 103:1 (July 7) 1934.

vent an adequate absorption of the essential food factors. Changes in the gastro-intestinal tract which may lead to the development of such conditions include atrophy of the mucous membrane, changes in the secretion of normal digestive juices or other substances, the absence of the bile salts, the loss of normal gastro-intestinal secretion, as in diarrhea and vomiting, and, last, mechanical factors which obstruct or prevent the contact of foods with a sufficient area of intestinal mucosa to permit adequate absorption.

The studies of Castle indicate that pernicious anemia is a deficiency disease in which the deficiency is the result, not of a defective diet, but usually of the absence from the gastric juices of a specific factor, which is not hydrochloric acid, pepsin, rennin or lipase. A number of cases have been described of a condition identical with pernicious anemia, in which there are various organic abnormalities of the digestive tract and in which occasionally the examination of the gastric juice reveals the presence of the so-called intrinsic factor of Castle.

Thus it seems to have been demonstrated that pernicious anemia may be the result of a lack of a digestive juice in the stomach, the absence from the diet of a substance previously thought to be closely related to vitamin G or the failure of absorption from the intestine of the product of interaction of the gastric juice and the extrinsic factor.

There are in the literature numerous reports of cases of deficiency states which apparently are the result of failure of adequate alimentation in the face of an apparently normal diet. This has been well established in the case of pellagra, which is observed to affect particularly patients who have carcinoma of the stomach and associated pyloric obstruction (Eusterman and O'Leary<sup>111</sup> and others). Night blindness attributable to a deficiency of vitamin A, which apparently is the result of inadequate absorption of the vitamins in the presence of a gastocolic fistula which side-tracked the small intestine, has been reported by Wilbur and Eusterman<sup>112</sup>. An instance of beriberi following entero-enterostomy in which all but 24 inches (60.9 cm.) of the small intestine was side-tracked has been recorded by Urmey and his associates<sup>113</sup>. Definite relief occurred after the administration of yeast, but complete relief was not obtained until the long blind loop of small intestine was restored to normal continuity.

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111 Eusterman, G. B., and O'Leary, P. A. Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastro-Intestinal Tract. Report of Thirteen Cases, *Arch Int Med* **47** 633 (April) 1931.

112 Wilbur, D. L., and Eusterman, G. B. Nutritional Night Blindness. Report of a Case, *J. A. M. A.* **102** 364 (Feb. 3) 1934.

113 Urmey, T. V., Ragle, B. H., Allen, A. W., and Jones, C. M. Beriberi Secondary to Short-Circuited Small Intestine, *New England J. Med.* **210** 251 (Feb. 1) 1934.

Strauss and his associates have presented evidence which indicates that multiple neuritis of the "alcoholic" type and that of pregnancy are actually deficiency states. Other diseases which are reported to be the result of inadequate intestinal absorption are osteomalacia and tetany in celiac disease and sprue, "achlorhydric anemia," which is caused by a deficiency of iron, the so-called "toxic state," which is associated with intestinal obstruction and pregnancy and which is the result of a loss of water and electrolytes, and nutritional edema, which is the result of inadequate absorption in intestinal tuberculosis.

Although factors of intestinal absorption are undoubtedly exceedingly important, as has been stressed, attention should be called to the fact that deficiency states may develop in patients who have gastrointestinal disease and who as a result of symptoms or of poor advice partake of an inadequate diet. The occasional development of scurvy in patients who are receiving treatment for peptic ulcer is a good demonstration of this fact.

There has been much interest in the effect of liquid petrolatum on the absorption of vitamin A and carotene because this substance is so widely used therapeutically. Earlier studies indicated that it has little influence on the absorption of these substances, but recently Dutcher and his collaborators<sup>114</sup> investigated the problem and came to the conclusion that the vitamin A potency of butter fat is lowered when butter fat is fed in small amounts in the presence of liquid petrolatum. With a larger amount of butter fat and a small amount of liquid petrolatum the deleterious effect of the latter is less marked, although still noted. The vitamin A potency of cod liver oil and its concentrates, on the other hand, is not adversely affected by liquid petrolatum. The explanation of this apparent discrepancy is that the carotene of butter is excreted in the unabsorbed liquid petrolatum, supposedly because of the greater solubility in the hydrocarbons of liquid petrolatum than in the lipids of the intestinal juices. The opposite is true of the solubility of vitamin A.

The absorption of iron from the intestinal tract cannot fail to be of interest to the clinician. The work of Heubner and Lintzel, as reviewed by Davidson and Leitch,<sup>102</sup> indicates that ferric iron is unlikely to remain for any length of time in a free state in the digestive tract, even in the absence of food because it combines with mucus. However, during digestion the combined effects of a low oxygen tension, an abundance of readily oxidizable organic substances and an acid reaction provide conditions in which the conversion of ferric iron to ferrous iron is more likely to occur than is the reverse. It is probable,

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114 Dutcher, R. A., Harris, P. L., Hartzler, Eva R., and Guerrant, N. V. Vitamin Studies. XIX. The Assimilation of Carotene and Vitamin A in the Presence of Mineral Oil, *J. Nutrition* 8:269 (Sept.) 1934.

therefore, that part at least of the soluble iron is reduced to ferrous iron, that only this part remains ionizable and absorbable and that absorption takes place as ferrous iron. Davidson and Leitch further pointed out that since the iron of food is wholly or chiefly ferric iron and because the availability of iron depends largely on the presence of acid in the stomach for its reduction to ferrous iron, there may be difficulty in liberating the iron of the food and in reducing it to ferrous iron in cases of achlorhydria. This in part may account for so-called "achlorhydric anemia" (hypochromic anemia) and suggests the importance of the administration of ferrous salts in its treatment.

## News and Comment

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### ELLA SACHS PLOTZ FOUNDATION FOR THE ADVANCEMENT OF SCIENTIFIC INVESTIGATION

The original purposes for which the Ella Sachs Plotz Fund was to be used were (1) researches directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery, (2) researches preferably on a single problem or on closely allied problems, it being hoped that investigators in this and other countries may be found whose work on similar or related problems may be assisted so that more rapid progress may be made possible, (3) for the purchase of apparatus and supplies that are needed for special investigations and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

In the past year the policy outlined in section 2 has been neglected. During the present great need for funds, grants will be given in the sciences closely related to medicine, without reference to special fields. The maximum size of the grants will usually be less than \$500.

During the eleventh year of the foundation eighty-three applications for grants were received by the trustees, forty of which came from the United States, and the other forty-three from thirteen countries in Europe, Asia and Africa. The total number of grants made during this year was twenty-seven, one of these being a continued annual grant. Fourteen of the new grants were made to scientists outside the United States.

In the eleven years of its existence the foundation has made two hundred and twenty-seven grants, and investigators have been aided in Argentina, Austria, Belgium, Chile, China, Czechoslovakia, Estonia, France, Germany, Great Britain, Hungary, Italy, Jugoslavia, Latvia, The Netherlands, Palestine, Poland, Portugal, Roumania, South Africa, Sweden, Switzerland, Syria and the United States.

Applications for grants for the year 1935-1936 should be sent to Dr Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, and must be in the hands of the executive committee before May 1, 1935. Letters asking for aid must state definitely the qualifications of the investigator, the character of the proposed research, the size of grant requested and the specific use of the money to be expended. Letters of recommendation from the directors of laboratories or clinics in which the work is to be done should be included.

### LEA AND FEBIGER PUBLISH MEMORIAL VOLUME

In recognition of one hundred and fifty years of publishing, Lea & Febiger have just made available a sketch originally prepared by Henry Charles Lea in 1885 to celebrate the one hundredth anniversary of the founding of their business, revised and amplified to bring it up to date. The volume is beautifully illustrated with facsimiles of letters and fine portraits. This company has been operated continuously by members of the same family. The first editor of the *Philadelphia Journal of the Medical and Physical Sciences*, established in 1820, later the *American Journal of the Medical Sciences*, was Nathaniel Chapman, who was also the first president of the American Medical Association. The publication became the *American Journal of the Medical Sciences* in 1827, under the editorship of Dr Isaac Hays, who was also in charge of the committee that prepared the *Principles of Ethics* of the American Medical Association. The company takes particular pride in its continuous publication in America of Gray's "Anatomy," beginning in 1859.

## SEVENTH INTERNATIONAL CONGRESS ON INDUSTRIAL ACCIDENTS AND DISEASES

The Seventh International Congress on Industrial Accidents and Diseases will be held at Brussels, Belgium, from July 22 to 27, 1935. The American committee of the congress is under the chairmanship of Dr. Fred H. Albee, New York, for the Section on Accidents, and that of Dr. Emery R. Hayhurst, Columbus, Ohio, for the Section on Industrial Diseases.

The American delegation to the congress will sail from New York on July 8 and will visit London, Amsterdam, The Hague and Paris and, optionally, Budapest. Physicians interested in the congress or in the medical tour in conjunction with it may address the secretary, Dr. Richard Kovacs, 1100 Park Ave., New York.

## SOUTHEASTERN SURGICAL CONGRESS

The sixth annual assembly of the Southeastern Surgical Congress (comprising Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee and Virginia) will be held in Jacksonville, Fla., March 11 to 13. Desired information may be procured from Dr. B. T. Beasley, secretary-treasurer, 1019 Doctors Building, Atlanta, Ga.

## Book Reviews

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**Physical Diagnosis** By Richard C Cabot Eleventh edition Price, \$5  
Pp 540, with 317 illustrations Baltimore William Wood & Company, 1934

The life history of any popular medical book is always of interest In 1900, Dr Richard Cabot, then an assistant in clinical medicine at the Harvard University Medical School, took it on himself to write a book on the physical diagnosis of diseases of the chest This book was intended for students, as Dr Cabot stated, it contained nothing original but endeavored to describe in simple concise English how the chest should be examined and to do away with certain well worn myths regarding physical diagnosis that had been carried onward in nearly all textbooks This volume was 310 pages long and contained among other novelties several roentgenograms of thoracic conditions bewilderingly difficult to appreciate and certainly impossible for the hard-headed clinician of those days to take seriously However, the book was a distinct contribution to American medicine It started teachers thinking how to improve clinical instruction

The book was deservedly popular, and in 1901 and 1903 it was reprinted In 1905, its title was changed to "Physical Diagnosis," and in order to cover this larger field it grew to be a volume 577 pages long It was still crisply written and differed from other books of the same kind by virtue of its strength of personality It made no attempt to describe technical processes with which Dr Cabot was unfamiliar and gave no space to the description of tests which he believed to be useless A review in the *Journal of the American Medical Association* (45 1185 [Oct 14] 1905) stated "The striking feature of Cabot's work is its individuality The personality of the author is felt on every page One is impressed with the fact that what is stated are the views of the author gained by personal experience and not those of someone else The strength of the book is in its honesty and in the courage of the writer and his shrewdness as a clinical observer and student Weight of authority does not prove to him the truth of a statement He must prove it by his own experience, and if this is at variance with the authority, well and good, the result goes down in print just the same Now, it is this critical spirit, this frank discussion of facts, this honest admission of his personal limitation, that livens the pages and makes one feel that one is having a heart-to-heart talk with the author For the practitioner, then, the book is highly entertaining and instructive, as well as for the student, if rightly used It is full of valuable hints"

Nearly thirty years later the eleventh edition of "Physical Diagnosis" is fresh from the press In form, it looks much like its progenitor, but has become a little better dressed and more costly It is written in the same personal manner Changes, of course, have crept in, for without doubt a certain amount of progress has been made with time in the art of physical diagnosis This is shown especially in the chapters on diseases of the heart and lungs, where much greater stress is laid on the roentgen rays and the electrocardiograms as significant aids to inspection, percussion, palpation and auscultation In the last edition, too, the author does not discuss laboratory procedures but limits himself more strictly to the proper interpretation of sign and symptoms

The reviewer of the first edition pointed out the chief weakness of the book It was incomplete in that such methods of physical examination as laryngoscopy, cystoscopy or ophthalmoscopy, with which Dr Cabot was unfamiliar, were not described The latest edition of the book makes no attempt to fill in these gaps It remains, however, a sturdy example of usefulness As it was in the beginning so it is now a highly entertaining and instructive book for the practitioner and student and full of valuable hints May it continue to have a successful career!

**Ergebnisse der Kreislaufforschung** Edited by Dr B Kisch Volume IV  
**Kreislaufstörungen und pathologische Histologie** By Dr Martin Nordman, Professor of General and Special Pathology at the University of Tübingen Price, paper, 13 80 marks, cloth, 15 marks Pp 174, with 14 illustrations Dresden Theodore Steinkopff, 1933

The treatment of the subject is from the point of view of histopathology About ten pages are devoted to the history of the subject After a brief review of the anatomy and physiology of the arteries, veins and lymph vessels, there is a brief discussion of the methods of investigation on living animals (capillary microscope, Sandison-Clark chamber and perfusion of organs) Then follows a detailed description of blood flow in the capillaries, smaller blood vessels and lymph vessels and the changes that these structures and the surrounding tissues undergo during normal variations, chemical stimulation, stasis, constriction and obstruction Some space is devoted to general peripheral circulation at different levels of pressure and to the rôle played by the viscosity of the blood, the reticulo-endothelial system and the "filter-system" following the injection of dyes and serum From this point on the author limits himself to the histopathology in man Under each topic is a short preliminary description of the histology involved, followed by a detailed discussion of the topic The material is divided into the following topics (1) edema, (2) suppuration, (3) diapedesis, (4) necrosis, (5) growth of (a) simple granulation tissue, (b) nodule-forming granulation tissue (in response to tuberculosis, syphilis, typhus, rheumatic nodules and foreign bodies, etc), (6) tissue repair, with a consideration of (a) atrophy, (b) scar formation, (c) chronic inflammation and (d) cirrhosis, (7) tumors (considered as an appendage), (8) cell and tissue metabolism under the headings fat, carbohydrate and protein, especially as it concerns the liver, thrombosis and amyloid and hyaline tissue The last chapter is devoted to the pathology of the arteries, veins and lymph vessels It considers arterial sclerosis, endarteritis obliterans, acute arteritis, aneurysms, hematomas, venous thrombosis, varicosities and elephantiasis A few pages are devoted to angiospasm The etiology of hypertension is discussed under neurogenic, hormonal and metabolic factors The pathology of hypertension is considered from the point of view of observation of living tissue as well as from that of histologic specimens Evidence is presented to show that the renal findings are the result, not the cause, of the hypertension The vascular changes during local and general infections, disturbances of the thyroid and anemia are correlated with previous findings Among his concluding remarks Nordman stresses the fact that the kind of stimulus is not as important as the strength of the stimulus in relation to the sensitivity of the body

This monograph treats of the physiology more than the pathology of the vascular system It is indexed and the bibliography, especially that of the European literature, is good It summarizes satisfactorily the work of the last eighty years on the pathology of the vascular system

**The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues** By F N Wilson, A G MacLeod and P S Barker Price, \$1 50 Pp 59 Ann Arbor, Mich University of Michigan Press, 1933

This monograph is an important contribution to electrophysiology The fundamental and comprehensive treatment of the distribution of electric currents resulting from the functional response of excitable tissues renders it of cardinal importance to all those dealing seriously with action potentials, whether in the field of electrocardiography or in other branches of physiology, namely, those dealing with the nervous and muscular systems and the electrical response of glands

The authors analyze the problem of the flow of current in a homogeneous medium, with particular reference to currents of action and injury of the cardiac muscle It is shown that the observed electrical phenomena can be simply explained on the hypothesis that the wave of excitation in the muscle is accompanied by an electrical source (positive) closely followed by a sink (negative) accompanying



the wave of excitation. A second sink followed by a source accompanies the wave of recovery, but inferences and experimental observations concerning it are developed in much less detail.

It is clearly pointed out that this interpretation is not only compatible with the Bernstein membrane hypothesis, but that it is a necessary consequence of it. In other words, the inferences as to source and sink imply nothing as to the detail of the mechanism or exact orientation of polarized membranes, etc., in the tissue. The electrical changes at a distant point are simply shown to correspond to what would occur if such sources and sinks were present, and reconciliation with the membrane hypothesis is complete.

Agreement with the experimental observations and most of the interpretations of Craib and disagreement with certain interpretations of Bishop and Gilson are expressed in a footnote. The exact basis for the criticisms of Bishop and Gilson is not explained in detail.

The monograph is useful as a simple exposition of the principles of the flow of current in volume conductors and should be helpful in the interpretation of the initial positive phase, sometimes called "positive artefact," preceding action potentials of nerve as well as muscle *in situ*.

The reviewing physiologists are grateful to the authors for relegating the mathematical derivations of the equations to an appendix, leaving in the text only those formulas which constitute the end-results of their efforts. The formulas are, happily, scattered through the text in such a way that the reader can hurdle them and read on without losing the thread of the argument.

### **Die akuten Zivilisationsseuchen, Ihre Epidemiologie und Bekämpfung**

By B. DeRudden. Price, 16 marks. Pp. 286, with 49 illustrations. Leipzig: Georg Thieme, 1934.

As DeRudden points out in his general introduction, the term *Seuche* is to be given its usually accepted modern definition, viz., a disease which attacks a large number of persons in a locality and which besides possesses the quality of endangering life. Under this title he considers in a clear, brief but eminently practical manner the infectious diseases—measles, smallpox, whooping cough, scarlet fever, diphtheria and poliomyelitis.

The book is divided into two main parts, the first being devoted to the epidemiology and the second to the methods of suppression and eradication. There are, of course, numerous tabulations which constitute the statistical data.

Any innovation, if such may be claimed for the work, lies not so much in the presentation of new material as in the arrangement of the material. There is no classification of the subject matter into chapters, but each main division is subdivided into discussions which follow each other in logical sequence and for this reason stimulate interest and make reading easy.

Some interesting points in the epidemiology are the figures and the descriptions of classic instances of acute infections afflicting a susceptible population, as, for example, the epidemics of measles among the people of Iceland and poliomyelitis ravaging the relatively small population of an island in the Pacific ocean. The author draws from these examples and from others conclusions that are worthy of more than a passing thought.

The section devoted to prophylaxis contains material of interest to students of preventive medicine, and its chief importance lies in the description of the methods employed and the results obtained by sanitarians and health officers in Central Europe.

A large part of the book has been read by the reviewer with keen interest and pleasure, and the work may be warmly recommended to those who desire to obtain an up-to-date insight into the general status of infectious diseases in the world, but more especially in Europe.

## RELATION OF PLASMA PROTEINS TO ASCITES AND EDEMA IN CIRRHOSIS OF THE LIVER

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AND

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In cirrhosis of the liver the accumulation of fluid in the peritoneal cavity is generally associated with a high degree of portal obstruction. This has been demonstrated repeatedly, but in a most convincing manner by McIndoe.<sup>1</sup> However, clinical observations suggest that other factors play important parts. The spontaneous variation of the amount of peritoneal fluid, the diminution of the ascites following the administration of diuretics and the changes subsequent to an alcoholic bout or an attack of dysentery are difficult to explain on the basis of portal obstruction alone.

Dependent edema of varying degree is frequently observed in patients with cirrhosis of the liver and portal obstruction. The edema of these patients has been explained on a basis of increased intra-abdominal pressure, causing obstruction of the venous return from the legs, or as a manifestation of cardiac failure. There are many patients concerning whom these explanations are inadequate. Edema of the dependent parts may be present in association with a minimal amount of fluid in the peritoneal cavity or without other evidence of circulatory failure. In these persons the edema commonly persists with rest in bed. It is evident that other explanations, aside from those cited, must be sought.

We have examined several other factors that contribute to the production of ascites and peripheral edema, including the blood plasma protein values, the protein content of the ascitic fluid and the effects of diets high in protein on the plasma protein levels.

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1 McIndoe, A H. Vascular Lesions of Portal Cirrhosis, *Arch Path* 5 23 (Jan) 1928.

## METHODS

Samples of blood were obtained repeatedly from sixteen patients with cirrhosis of the liver. In the cases in which the ascitic fluid was withdrawn for study, the specimens of blood were collected immediately preceding the abdominal paracentesis. In view of the changes in the blood plasma following paracentesis, it was necessary to withdraw the blood before rather than after abdominal tapping in order to obtain comparable conditions and results.

In addition to the patients with cirrhosis of the liver, fourteen others with various types of disease of the liver were studied for comparison.

Potassium oxalate was added to the samples of blood and ascitic fluid to prevent coagulation. The amounts of potassium oxalate were kept constant, so that variation in the values of protein as the result of the action of the oxalate on cell volume, as shown by Peters, Eisenman and Bulger,<sup>2</sup> would be comparable.

The plasma protein value was calculated from the protein nitrogen as determined after subtracting the nonprotein nitrogen from the total nitrogen content of the plasma. The total nitrogen content of each sample of plasma or ascitic fluid was determined in duplicate by a macro-Kjeldahl method.

The globulin of the plasma, or ascitic fluid, was precipitated by means of a buffer solution of  $p_H$  7 of potassium di-hydrogen phosphate and di-potassium hydrogen phosphate. The nitrogen content of the filtrate was likewise determined in duplicate by the macro-Kjeldahl method. From the total nitrogen, the nonprotein nitrogen and the filtrate nitrogen were calculated the values for the albumin fraction, the globulin fraction and the albumin-globulin ratio of the plasma or ascitic fluid.

## RESULTS OF THE STUDY OF THE BLOOD PLASMA PROTEINS

In the sixteen patients with cirrhosis of the liver without albuminuria, the plasma protein values were determined in forty-nine instances. The results are summarized in table 1. Fourteen patients presented the signs of uncomplicated cirrhosis of the liver, in the other two the condition was complicated by tuberculosis of the peritoneum. Fifteen had ascites, and in seven abdominal paracentesis had been done on several occasions before the studies were begun. Thirteen showed peripheral dependent edema. The diagnosis was confirmed by necropsy in seven cases.

In patient 1, neither ascites nor edema was observed, but the diagnosis was confirmed at necropsy. In patient 2, the amount of free fluid was so slight that its removal was unnecessary. Patient 10 showed massive peripheral edema and barely demonstrable ascites. An old alcoholic cirrhosis of the liver was found at autopsy. The plasma protein values were studied at frequent intervals in patients 4 and 9 during spontaneous remissions, that is, during a period when there was marked diuresis, with a decrease in the amount of ascitic fluid and peripheral edema. Later, a reaccumulation of the fluid was observed in patient 4. In another patient, the plasma protein values were studied at intervals following paracentesis. The results are summarized in table 1.

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<sup>2</sup> Peters, J. P., Eisenman, A. J., and Bulger, H. A. The Plasma Proteins in Relation to Blood Hydration. I. In Normal Individuals and in Miscellaneous Conditions, *J. Clin. Investigation* 1: 435 (June) 1925.

TABLE 1—*Plasma Proteins in Sixteen Patients with Cirrhosis of the Liver*

Patient	Date	Total Plasma Protein, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globulin, Gm per 100 Cc	Albumin Globulin Ratio	Leucocytes	Jaundice	Edema	Comment
1		5.7	2.45	3.25	0.754	—	+	—	Rapidly progressive, fibrinogen, 0.226 Gm per 100 cc, autopsy, alcoholic cirrhosis
2		5.5	1.43	4.07	0.351	+	+	—	Early cirrhosis, improved with diuretics, no paracentesis
3		4.6	2.21	2.39	0.923	+	+	+	Rapid course to death, no previous paracentesis, autopsy, alcoholic cirrhosis
4	10/29	5.9	2.07	3.53	0.638	+	—	+	No previous paracentesis
	2/28	5.9	1.72	4.18	0.408	+	—	±	
	3/24	5.6				+	—	±	Salyrgan with good results
	4/20	6.8	2.52	4.28	0.587	+	—	—	Salyrgan with good results
	5/ 5	6.2	2.05	4.15	0.492	+	—	—	Spontaneous diuresis
	5/17	7.1	2.63	4.47	0.587	±	—	—	Diet of 180 Gm protein daily started
	6/ 5	5.9	2.66	3.24	0.818	+	—	—	Diet of 180 Gm protein daily continued
5	5/ 5	4.8	1.78	3.02	0.587	+	—	+	Duration of illness six weeks, two previous paracenteses
	5/14	4.8	2.11	2.69	0.785	+	—	+	
	5/28	4.6	2.07	2.53	0.818	+	—	+	
	6/ 8	4.4	2.08	2.32	0.923	+	—	+	Salyrgan, diet of 100 Gm protein
	6/21	4.7	2.02	2.68	0.754	+	—	+	Salyrgan
	6/30	4.6	2.16	2.44	0.886	+	—	+	
	7/17	4.7	2.07	2.63	0.785	+	—	+	Fibrinogen, 0.442 Gm per 100 cc
	7/24	4.8	2.16	2.64	0.818	+	—	+	
	7/27	4.3	1.76	2.54	0.695	+	—	+	Diet of 100 Gm protein continued
6	8/28	5.2	1.72	3.48	0.492	+	—	+	Several previous paracenteses, autopsy, alcoholic cirrhosis
7	2/11	4.6	1.93	2.67	0.724	+	—	±	Eight previous paracenteses
	2/23	4.8	1.78	3.02	0.587	+	—	+	
	3/ 4	4.4	1.67	2.73	0.613	+	—	+	
	3/19	4.4	1.72	2.68	0.639	+	—	+	
	3/30	4.6	1.84	2.76	0.667	+	—	+	
	4/11	4.6	1.93	2.67	0.724	+	—	+	Diet of 180 Gm protein started before paracentesis
	4/11	4.0	1.68	2.32	0.724	+	—	+	6 hours after paracentesis
	4/12	4.1	1.64	2.46	0.667	+	—	+	18 hours after paracentesis
	4/14	4.3	1.72	2.58	0.667	+	—	+	72 hours after paracentesis
	4/21	4.4	1.80	2.60	0.695	+	—	+	
	5/ 9	4.2	1.85	2.35	0.785	+	—	+	Diet high in protein discontinued readmission
	7/19	4.7	1.88	2.82	0.667	+	—	+	Readmission
	10/ 2	4.9	1.81	3.09	0.587	+	—	+	Readmission
	10/ 4	4.8	1.82	2.98	0.613	+	—	+	Autopsy, alcoholic cirrhosis
8	1/ 4	5.3				+	+	+	No previous paracentesis
	1/29	5.8	1.62	4.18	0.388	+	±	+	Paracentesis
	2/23	5.8	1.45	4.35	0.333	+	—	+	Paracentesis, diet of 180 Gm protein daily from 2/3
	4/ 4	5.4	1.57	3.83	0.408	+	—	+	Diet of 300 Gm protein daily from 2/23
9	12/ 7	5.1	1.94	3.16	0.612	+	±	+	Cirrhosis present for 4 years, no paracentesis, diet of 60 Gm protein daily
	12/15	5.9	2.36	3.54	0.667	+	—	±	Spontaneous diuresis, decrease of edema and ascitic fluid, diet of 60 Gm protein daily
10		3.8	1.90	1.90	1.000	+	—	+	No paracentesis, massive edema, autopsy, alcoholic cirrhosis, little ascites
11		5.0	2.30	2.70	0.852	+	—	±	Died, no autopsy
12		5.1	2.09	3.01	0.695	+	+	+	Two previous paracenteses
13		5.7	1.30	4.40	0.298	+	+	+	Purpura, one previous paracentesis
14		5.2				+	—	+	Three previous paracenteses, autopsy, alcoholic cirrhosis
15	4/ 4	6.1	2.48	3.62	0.639	+	—	±	No previous paracentesis
	4/10	6.1	2.32	3.78	0.613	+	—	±	Autopsy, alcoholic cirrhosis, tuberculous peritonitis
16	2/10	5.7				+	—	—	No previous paracentesis
	2/22	5.9	2.36	3.54	0.667	+	—	—	Cirrhosis, tuberculous peritonitis (inoculation of guinea pigs)

From table 1 it is seen that the plasma protein values in fourteen patients were consistently below the normal level of from 6 to 8 Gm per hundred cubic centimeters. In but five observations, and these were on plasma from two patients, was the value 6 Gm or higher. Indeed, in five patients the determinations were constantly 5 Gm per hundred cubic centimeters or lower. The albumin-globulin ratio was inverted. The values ranged between 0.298 and 1. The values for the albumin fraction, therefore, were low. The albumin fraction was below 2.5 Gm per hundred cubic centimeters in every instance, except in patient 4, in whom the albumin was over 2.5 Gm, only during the period of remission.

TABLE 2—*Plasma Proteins in Fourteen Patients with Various Disorders of the Liver*

Patient	Total Plasma Protein, Gm per 100 Cc	Albumin Fraction, Gm per 100 Cc	Globulin Fraction, Gm per 100 Cc	Albumin Globulin Ratio	Comment
17	6.2	2.23	3.97	0.562	Toxic cirrhosis
18	5.8	3.71	2.09	1.778	Arsphenamine hepatitis
19	5.9	3.48	2.42	1.439	Arsphenamine hepatitis
20	6.0	2.82	3.18	0.886	Arsphenamine hepatitis
21	6.3	3.81	2.49	1.632	Catarrhal jaundice, three weeks
22	5.7	3.42	2.28	1.500	Catarrhal jaundice, ten days
23	5.9	3.44	2.46	1.500	Catarrhal jaundice, ten days
24	5.8	2.93	2.87	1.020	Catarrhal jaundice, six weeks
25	6.4	3.01	3.39	0.886	Liver and spleen enlarged, hemachromatosis (?)
26	5.5	3.30	2.20	1.500	Liver and spleen enlarged, hemachromatosis (?)
27	6.1	2.98	3.12	0.961	Liver and spleen enlarged, cirrhosis of liver (?)
28	7.9	1.58	6.32	0.250	Liver and spleen enlarged, jaundice, ascites, edema one year previously, biopsy, healed acute yellow atrophy
29	7.7	3.47	4.23	0.818	Carcinoma of colon, few metastases to liver, no edema
30	5.3	2.28	3.02	0.754	Carcinoma of stomach, metastases to liver, jaundice, ascites, edema (nutritional)

In table 2 are shown the results of determinations of the plasma proteins, albumin fraction, the globulin fraction and the albumin-globulin ratio in fourteen patients with hepatic lesions. The condition of one patient, with a history of chronic alcoholism, syphilis and arsphenamine therapy, who had a small liver, a large spleen, jaundice and ascites, was diagnosed toxic cirrhosis. The albumin-globulin ratio was inverted and the albumin fraction was correspondingly low. The plasma from three other patients with arsphenamine hepatitis was studied. The total plasma protein values were found to be near the lower limits of normal, and one patient had a low albumin content and an inverted albumin-globulin ratio.

Determinations were made on the plasma from four cases with a diagnosis of catarrhal jaundice. The total protein values were decreased. Only one of the four patients had much change in the albumin fraction. The plasma from this patient was obtained during convalescence, after a

prolonged illness Wiener and Wiener<sup>3</sup> noted in catarrhal jaundice rather high plasma protein levels owing to an increase in the globulin fraction accompanied by a slight decrease in the albumin fraction

TABLE 3—*Proteins of Ascitic Fluid from Twelve Patients with Cirrhosis of the Liver*

Patient	Date	Total Protein, Gm per 100 Cc	Albumin Fraction, Gm per 100 Cc	Globulin Fraction, Gm per 100 Cc	Albumin Globulin Ratio	Amount Removed, Liters	Specific Gravity	Total Protein Removed, Gm	Albumin Removed, Gm	Globulin Removed, Gm	Number of Abdominal Paracenteses
3		1.0	0.49	0.51	0.961	7.00		70.0	34.30	35.70	1
4	10/29	1.5	0.71	0.79	0.886	5.75	1.012	86.2	40.82	45.42	1
5	5/5	0.7	0.31	0.39	0.785	4.04	1.007	28.3	12.44	15.84	3
	5/14	0.9	0.50	0.40	1.272	3.75	1.007	53.7	18.90	14.85	4
	5/28	0.8	0.43	0.37	1.173	3.80	1.008	30.4	16.40	14.00	5
	6/21	0.9	0.47	0.43	1.083	5.80	1.008	52.2	27.14	25.06	6
	7/17	1.0	0.60	0.40	1.500	4.91		49.1	29.46	18.64	7
	7/21	1.0	0.54	0.46	1.173	7.41	1.007	74.0	39.96	34.04	8
6	8/1	0.1				8.00	1.008	8.0			4
	8/28	0.6				6.40	1.008	38.4			5
7	2/23	1.2	0.54	0.66	0.818	16.00	1.008	199.2	89.64	109.56	10
	3/4	1.0	0.47	0.53	0.886	15.00	1.004	150.0	70.70	79.30	11
	3/12	0.8	0.36	0.44	0.818	13.60	1.008	112.9	50.80	72.07	12
	3/19	0.8	0.36	0.44	0.816	14.10	1.010	114.2	51.40	62.81	13
	3/30	1.0	0.44	0.56	0.785	13.85	1.008	138.5	60.94	77.56	14
	4/11	1.3	0.60	0.70	0.852	16.00	1.012	208.0	95.68	112.32	15
	4/21	1.3	0.59	0.71	0.818	12.50	1.007	162.5	73.12	99.37	16
	5/9	1.4	0.67	0.73	0.923	13.50	1.008	189.0	90.72	98.28	17
	5/19	1.0	0.37	0.63	0.587	13.50	1.006	135.0	49.95	85.05	18
	5/24	0.8	0.40	0.40	1.000	7.50	1.007	60.0	30.00	30.00	19
	7/19	0.6	0.29	0.31	0.961	14.00	1.010	84.0	41.16	42.84	23
	10/2	0.5	0.19	0.31	0.613	12.00	1.010	60.0	22.80	37.20	25
	10/5	0.4	0.21	0.19	1.010	12.00	1.008	4.8	2.50	2.30	29
8	1/8	1.1				7.20	1.002	79.2			1
	1/29	1.3	0.60	0.70	0.852	10.00	1.005	130.0	60.00	70.00	2
	2/23	1.3				12.00	1.005	156.0			3
	3/14	1.7				12.00	1.009	204.0			4
11	10/1	0.7	0.47	0.23	2.030						1
	11/10	0.6				8.00					4
12	7/27	1.3	0.69	0.61	1.128						
13	5/2	0.8	0.23	0.57	0.408	4.50	1.009	34.2	9.90	24.30	2
	9/14	0.7	0.39	0.31	1.220	7.60	1.007	73.2	29.30	23.90	3
14	7/16	0.9				13.00	1.015	117.0			3
15	4/10	3.2	1.54	1.66	0.923	6.00	1.014	144.0	69.12	74.88	1*
16	2/22	4.4	2.55	1.85	1.381	8.00	1.015	352.0	205.16	147.84	1*

\* Tuberculous peritonitis

Specimens of plasma from four patients with hepatomegalia and splenomegalia, two with a clinical diagnosis of hemachromatosis, were examined. No constant observations were made, although one patient had a slightly low total plasma protein value and two patients showed a

slightly decreased albumin fraction with corresponding alterations in the albumin-globulin ratio. One of the four showed a much reduced albumin fraction and an increased globulin fraction in the absence of ascites or edema, but one year previously he had had jaundice, ascites and peripheral edema. Biopsy of the liver revealed healed acute yellow atrophy.

There were two patients with metastatic carcinoma of the liver. One showed but few metastases at autopsy, and during life had had no anasarca and a normal total plasma protein value with an inverted albumin-globulin ratio, the result of an increase in the globulin fraction. The second patient had a low total plasma protein value with a low albumin fraction and an inverted albumin-globulin ratio. This patient had moderately extensive anasarca, malnutrition was an important factor.

In patients with cirrhosis of the liver, the total plasma protein values were reduced. This reduction in total plasma proteins was particularly at the expense of the albumin fraction. The globulin fraction was normal or slightly increased. The albumin-globulin ratio was correspondingly inverted. In patients with less severe hepatic damage the plasma protein determinations showed less marked alterations. The values for total plasma proteins were either normal or slightly reduced. The albumin fraction was occasionally below the lower normal values. The globulin fraction was frequently increased.

#### RESULTS OF THE STUDY OF THE ASCITIC FLUID

The protein content of thirty-five samples of ascitic fluid removed from the twelve patients on whom plasma protein studies were made are summarized in table 3. The total protein values, albumin fraction, globulin fraction and albumin-globulin ratio were determined. Also, the loss of protein, albumin and globulin was calculated from the amount of ascitic fluid removed by paracentesis. The fluid from two patients who had tuberculous peritonitis complicating hepatic cirrhosis contained 3.2 and 4.4 Gm. of protein per hundred cubic centimeters. The total protein content of the fluid of patients with uncomplicated hepatic cirrhosis varied between 0.1 and 1.7 Gm. per hundred cubic centimeters. The values obtained in these samples of ascitic fluid are in agreement with the findings of Loeb, Atchley and Palmer,<sup>4</sup> Foord, Youngberg and Wetmore<sup>5</sup> and Barnett, Jones and Cohn.<sup>6</sup> The loss of protein as a result

<sup>4</sup> Loeb, R. F., Atchley, D. W., and Palmer, W. W. On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, *J. Gen. Physiol.* **4**: 591, 1922.

<sup>5</sup> Foord, A. G., Youngberg, G. E., and Wetmore, V. The Chemistry and Cytology of Serous Fluids, *J. Lab. & Clin. Med.* **14**: 417 (Feb.) 1929.

<sup>6</sup> Barnett, C. W., Jones, R. B., and Cohn, R. B. The Maintenance of a Normal Plasma Protein Concentration in Spite of Repeated Protein Loss by Bleeding, *J. Exper. Med.* **55**: 683 (May) 1933.

of abdominal paracentesis in patients with uncomplicated cirrhosis of the liver was occasionally found to exceed 200 Gm at one time. The average calculated daily loss for the patients repeatedly studied was usually less than 10 Gm, but occasionally was as much as 18 Gm.

The albumin-globulin ratios were found to vary within wide limits. The albumin-globulin ratio of the proteins of the fluid consistently was higher than that of the corresponding plasma proteins. A larger proportion of the albumin fraction than of the globulin fraction had passed into the ascitic fluid.

In summary, the ascitic fluid removed from patients with uncomplicated cirrhosis of the liver contained from 0.1 to 1.7 Gm of protein per hundred cubic centimeters. The albumin fraction of the proteins of the ascitic fluid was relatively greater than that of the plasma proteins, that is, the albumin-globulin ratio of the proteins of the ascitic fluids was higher than that of the plasma proteins.

#### EFFECT OF PROTEIN FEEDING ON THE PLASMA PROTEINS

In an effort to determine whether the blood plasma proteins could be increased by a diet high in protein, food containing large amounts of protein was given to four patients. Patient 4 showed a decrease in the plasma proteins during a period of two weeks while ingesting 180 Gm of protein a day. During two weeks preceding the diet high in protein, the patient had had spontaneous diuresis with a resultant decrease of ascites and edema. The relationship between the fluid intake and urinary output was reversed within a few days after the diet high in protein was started. Patient 5 was unable to eat all the protein food offered because of anorexia. Patient 7 received food containing 180 Gm of protein daily for four weeks. The diet was well taken.

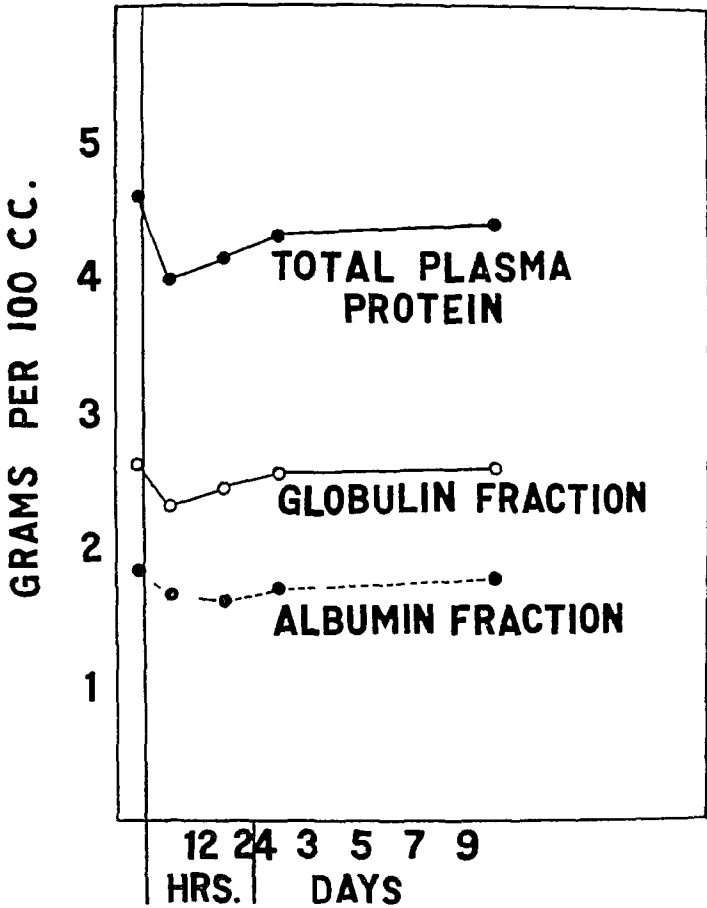
No effect on the plasma protein content was demonstrated, such as is usually observed when diets high in protein are given patients with hypoproteinemia resulting from dietary deficiency, indeed, in this case, the total plasma protein content fell from 4.6 to 4.2 Gm per hundred cubic centimeters during the period of forced feeding of protein. Patient 8 received a diet which contained approximately 180 Gm of protein daily for three weeks. There was no essential change in the plasma protein values. For the following six weeks, 300 Gm of protein was ingested daily. There was a slight decrease in the globulin fraction of the plasma proteins. From the observations on these few patients the hypoproteinemia of hepatic cirrhosis does not seem to be a result of dietary deficiency. Experiments on nitrogen balance were not carried out to determine the proportion of ingested protein which was digested and absorbed. There was no excess of undigested meat fibers in the stools. The determination of the nitrogen content of the stools was carried out



in patient 8 during the periods when 180 Gm and 300 Gm of protein were ingested The daily loss of nitrogen in the stools was 1.26 and 1.16 Gm per day, respectively

IMMEDIATE EFFECT OF ABDOMINAL PARACENTESIS ON THE PLASMA PROTEIN VALUES

It was repeatedly noted, even by the patient, that an appreciable decrease in the peripheral edema and marked diuresis took place follow



Changes in the plasma proteins following the removal of ascitic fluid in patient 7

ing the removal of ascitic fluid The plasma protein values were determined at intervals following paracentesis in patient 7 The changes are shown in the figure and are recorded in table 1 As noted previously by Bernard,<sup>7</sup> there was a profound disturbance in the water metabolism The albumin and globulin fractions were reduced proportionately at

7 Bernard, E Dilution et concentration sanguines apres les ponctions d'ascites L'etape sanguine de la fonte des oedemes, Semaine d hôp de Paris 6 581 (Dec 15) 1930

first. Later, the globulin fraction of the plasma rose and did so more rapidly than the albumin fraction. Thus, following paracentesis there may be diuresis accompanied by further reduction of the total protein value of the serum possibly due to dilution of the blood plasma.

## COMMENT

From our observations it is evident that a considerable number of patients with cirrhosis of the liver show a definite decrease in the total plasma proteins. The albumin fraction was consistently decreased, and the albumin-globulin ratio was inverted. These observations are in accord with those of others.<sup>8</sup> It was also clear that the patients with peripheral edema as well as ascites commonly showed a decrease in the total plasma proteins, showing that this factor was of importance in explaining the presence of peripheral edema.

In seeking an explanation for the low plasma protein values in these cases, three factors were considered: an inadequate intake or absorption of protein, defective formation of plasma proteins and a loss of protein from the blood stream into the ascitic fluid.

To test whether an inadequate intake or absorption of protein was responsible for the low plasma protein content, four patients were given large amounts of protein, from 100 to 300 Gm. a day, but it was impossible to increase the proteins of the blood. While malnutrition may play a part in some patients with cirrhosis, this did not seem to be the case, at least in the four patients who were given diets liberal in protein. Although studies of the nitrogen balance were not made, observation suggested no loss of ingested proteins in stools. When there is prolonged decreased protein intake, the addition of liberal amounts of protein to the diet causes an increase of the blood proteins. In the cases of cirrhosis, the plasma proteins were not increased as a result of available dietary proteins. It was manifest then that an inadequate intake could not explain our observations. The other two factors, namely, defective formation and loss of protein from the blood stream into the ascitic fluid, were of more importance.

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8 (a) Gilbert, A., and Cheray, M. Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, *Mem Soc de biol* **63** 487, 1907. (b) Grenet, H. Diminution des albumines du serum sanguin chez les hépatiques, *Mem Soc de biol* **63** 532, 1907. (c) Salvesen, H. A. Variations in the Plasma Proteins in Nonrenal Conditions, *Acta med Scandinav* **72** 113, 1929. (d) Abram, P., and Robert-Wallech. Modifications du serum sanguin du foie avec ascites. Inversion du rapport sérums-globulines, *Compt rend Soc de biol* **101** 291 (May 25) 1929. (e) Peters, J. F., and Eisenman, A. J. The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, *Am J M Sc* **186** 808 (Dec.) 1933. (f) Wiener and Wiener.<sup>3</sup> (g) Barnett, Jones and Cohn.<sup>6</sup>

Thompson, Ziegler and McQuarrie<sup>9</sup> and Myers and Taylor<sup>10</sup> have indicated that hypoproteinemia may develop as a result of defective formation of blood proteins. That this mechanism is of importance in cirrhosis of the liver is suggested by two observations: first, our inability to raise the level of the blood proteins by high protein feeding and, second, the fact that the blood protein may be decreased in disease of the liver without ascites or edema. This explanation also has been suggested by Grenet,<sup>8b</sup> Jollis<sup>11</sup> and Salvesen.<sup>8c</sup> It has been shown by Sawada<sup>12</sup> that following hepatic damage in rabbits there is a decrease in the serum albumin and fibrinogen and an increase in serum globulin. We found that patients with limited cirrhosis showed a decrease in the serum albumin and a slight increase in the serum globulin. In patients with more extensive cirrhosis, the albumin fraction was considerably decreased, and the globulin fraction was approximately normal.

There remains for discussion the factor of the loss of protein into the ascitic fluid. We have said that this protein was relatively rich in albumin. The total amount of protein in the ascitic fluid was, in many cases, considerable. In some instances, as much as 200 Gm. was removed at one time, and in a few cases the daily calculated loss was as much as 18 Gm. of protein.

The removal of a comparable amount of protein from dogs by plasmaphoresis results in only transient hypoproteinemia. For example, Barnett, Jones and Cohn<sup>6</sup> found that the removal of 5.2 Gm., or 0.41 Gm. of protein per kilogram of body weight, from a dog every day for six weeks failed to produce a deficiency of plasma protein.

In the cases we observed, repeated abdominal paracentesis with the loss of large amounts of protein did not lead to a progressive decrease in the total plasma protein or in the albumin or globulin fraction. In spite of this loss and high protein feeding, the plasma proteins were maintained at a low level. This state of affairs is not reproduced in the dog, in which the loss is accompanied by protein feeding.

From what has been said, it seems justifiable to conclude that the low plasma protein values in cirrhosis of the liver are the result of the loss of protein into the ascitic fluid together with defective formation of plasma proteins. In most instances a diet low in protein and a lack of absorption are not contributing factors. The ascites, then, would

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9 Thompson, W. H., Ziegler, M., and McQuarrie, I. A Comparative Study of the Inorganic Metabolism in Nephrosis and in Edema of Undetermined Origin, *Am J Dis Child* **44** 650 (Sept.) 1932.

10 Myers, W. K., and Taylor, F. H. L. Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins, *J A M A* **101** 198 (July 15) 1933.

11 Jollis, quoted by Grenet<sup>8b</sup>.

12 Sawada, T. Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, *Jap J Gastroenterol* **3** 38 (April) 1931.

appear to result from increased hydrostatic pressure in the portal vein and a low plasma protein level. The dependent edema can be explained in part by the presence of the low blood plasma protein content and increased venous pressure. The latter can occur only in the presence of massive ascites.

#### SUMMARY

Sixteen cases of cirrhosis of the liver were studied. A deficiency in the total plasma protein was found. The decrease was most pronounced in the albumin fraction. The albumin-globulin ratio was inverted.

Similar but less extensive and less consistent alterations in the plasma protein values were observed in fourteen cases of other forms of disease of the liver.

In patients with cirrhosis of the liver the following conditions were observed:

1. The protein content of ascitic fluid varied between 0.1 and 1.7 Gm per hundred cubic centimeters. The albumin content of the ascitic fluid was proportionately greater than that of the blood plasma.

2. The removal of ascitic fluid gave rise to changes in the plasma protein value and a temporary hydremia with corresponding diuresis.

3. Peripheral edema without circulatory failure was associated with a reduction of the plasma proteins.

In cirrhosis of the liver the appearance of ascites must depend somewhat on the osmotic pressure of the blood plasma as well as on portal obstruction. The hypoproteinemia may arise from a defective formation of plasma proteins and a loss of protein into the ascitic fluid. The defect may be due to alteration in the function of the liver.

# NITROGEN AND SULPHUR METABOLISM IN BRIGHT'S DISEASE

## VI EFFECT OF DIETS LOW IN SULPHUR ON THE EXCRETION OF SULPHUR

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These studies were initiated in the attempt to utilize the effects of iodides and salicylates on the excretion of nitrogen and sulphur<sup>1</sup> in the study of Bright's disease. It has been shown previously that iodides and salicylates mobilize different types of nitrogen and that the effect of iodide is produced by the mediation of the thyroid gland<sup>2</sup>. When an attempt was made to conduct similar studies on patients with renal disease, it was observed that patients with the nephrosis syndrome showed a relationship between the amount of nitrogen and the amount of sulphur excreted in the urine similar to that exhibited by persons as an effect of the administration of iodides, whereas patients with other types of renal disease showed a totally opposed relationship between these two urinary constituents. Further studies indicated that the reaction to iodides and salicylates in patients with Bright's disease<sup>3</sup> was different from that exhibited by normal persons, but owing to a variety of factors the results were not sufficiently regular to warrant statistical comparison.

In brief, patients with edema of renal origin tend to retain sulphur<sup>4</sup> to an even greater extent than nitrogen, whereas patients without renal

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From the medical clinic of the Peter Bent Brigham Hospital

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1 Grabfield, G P. The Action of Iodides on the Nitrogen Metabolism, Boston M & S J **197** 1121, 1927. Grabfield, G P, and Knapp, E. The Effect of Salicylates on the Nitrogen Metabolism with Special Reference to the Effect of the Cation of the Salt, J Pharmacol & Exper Therap **32** 341, 1928.

2 Grabfield, G P, Flower, B, Gray C, and Knapp, E. The Mechanism of the Action of Iodides on the Nitrogen Metabolism, J Clin Investigation **4** 323, 1927.

3 Grabfield, G P. The Effect of Iodides on the Nitrogen and Sulphur Metabolism in Bright's Disease, J Pharmacol & Exper Therap **42** 253, 1931.

4 Grabfield, G P. Studies on the Nitrogen and Sulphur Metabolism in Bright's Disease. I Retention of Nitrogen and Sulphur in "Nephrosis," J Clin Investigation **9** 311, 1930.

edema tend to have a negative sulphur balance.<sup>5</sup> Whether the opposing behavior of the excretion of sulphur in the two types of nephritis is a part of the same mechanism, we have so far been unable to determine. It is obvious, however, that some special mechanism is at work, because the content of nonprotein constituents of the blood under the two sets of circumstances would lead one to suspect that the reverse would occur. Wakefield and Keith,<sup>6</sup> Wakefield,<sup>7</sup> Loeb and Benedict,<sup>8</sup> and others have shown that the patient in whom the metabolic sulphur balance becomes negative may, and frequently does, have a high level of inorganic sulphate in the protein-free blood filtrate, whereas Keith has shown that the content of inorganic sulphate in patients with the nephrosis syndrome tends to be low, like the content of blood urea. That this behavior of the sulphur is a special mechanism present in Bright's disease and is not associated merely with edema has been shown by the study of a patient with edema of unknown, but nonrenal, origin who had a persistent negative sulphur balance.<sup>9</sup>

It was the object of the present study to find a method of varying the intake of sulphur independent of the intake of nitrogen. In considering methods of accomplishing this, we decided not to attempt to increase the sulphur intake by feeding products containing sulphur, because this will constitute a special problem to be considered in another group of experiments. On the other hand, the use of gelatin enabled us to diminish the intake of sulphur without varying the intake of nitrogen, and we were able in that way to reduce the intake of sulphur to about 100 mg. a day. The feeding of gelatin has the obvious disadvantage that it is an incomplete protein and cannot provide completely for the needs of the body. It is evident from Robison's figures<sup>10</sup> and from his extensive study of the biologic value of various proteins<sup>11</sup> that gelatin can be used only partly to provide the protein in protein-free diets. It may be, therefore, that in these experiments the factor of

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5 Grabfield, G. P. Studies on the Nitrogen and Sulphur Metabolism in "Bright's Disease." II. Observations on the Nitrogen and Sulphur Excretion in Patients without Renal Edema, *J. Clin. Investigation* **10** 309, 1931.

6 Wakefield, E. G., and Keith, N. M. A Study of Inorganic Sulphates in Relation to Acid-Base Equilibrium in Renal Insufficiency and "Renal Acidosis," *J. Clin. Investigation* **9** 19 (Aug.) 1930.

7 Wakefield, E. G. Inorganic Sulphates in Renal Insufficiency, *Arch. Int. Med.* **44** 244 (Aug.) 1929.

8 Loeb, R. F., and Benedict, E. M. Inorganic Sulphates in Human Blood, *J. Clin. Investigation* **4** 33, 1927.

9 Grabfield, G. P., Driscoll, M., and Gray, M. G. Nitrogen and Sulphur Metabolism in Bright's Disease. V. Metabolic Study of a Patient with Edema of Unknown Origin, *Arch. Int. Med.* **54** 764 (Nov.) 1934.

10 Robison, R. Gelatine as a Food Stuff, *Biochem. J.* **16** 111, 1922.

11 Robison, R., and Martin, C. J. On the Biological Value of Certain Proteins, *Biochem. J.* **16** 407, 1922.

protein starvation must be taken into account, but, in any case, the starvation was complete only so far as the sulphur was concerned. In our experiments the nitrogen balance reacted in a manner similar to that of Robison's normal subjects.

We used three day periods in order to make our results comparable with those of our previous experiments and because our experience showed that sick patients cannot tolerate the somewhat unpleasant diet of gelatin for a longer period. While such a period is short, it yields results that are interpretable. The patients were fed whatever diet seemed appropriate from a therapeutic point of view. After the excretion reached a level all the protein in the food was provided by gelatin for a three day period, the caloric and nitrogen value of the diet remaining unchanged. The diet was carefully weighed, and the food refused was weighed. The water in the food was taken into account, and the intake of fluid was adjusted so that the total intake of fluid amounted to 2,500 cc per day. The patients were all in bed, and the caloric value of the diet was from 1,500 to 2,000 per day. We studied three consecutive three day periods, and the studies included examination of the total nitrogen, the total sulphur and the creatinine of the urine. Analysis of the feces was not done for technical reasons, and it has been found that no material information is added by such analyses.<sup>12</sup>

Unfortunately, the available patients formed a rather mixed group, consequently it is probably best to consider each one separately. For control observations we studied two patients (cases 13 and 14) who had good renal function and whose chief difficulty was hypertension. Neither had edema during the period of study, in neither case was the serum protein determined, because it was not considered that it was lowered. Table 1 shows the effect of the gelatin diet in these patients, and shows only a slight attempt to reduce the excretion of sulphur in response to the low intake of sulphur. We were particularly anxious to use these patients because Robison, in his careful studies, was unable to publish his figures on sulphur,<sup>13</sup> and these patients may in a sense be taken as normal controls. There was a definite but very slight tendency to a reduction in the excretion of sulphur in response to the sulphur-poor diet. Both patients used for controls showed diuresis during the gelatin feeding, which tended to increase the urinary excretion of sulphur.<sup>14</sup> However, the negative sulphur balance during the period of the gelatin diet amounted to 700 mg on the average.

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<sup>12</sup> Grabfield, G. P. Unpublished data.

<sup>13</sup> Robison, R. Personal communication to the authors.

<sup>14</sup> Fowler, C. C., and Hawk, P. B. Studies on Water Drinking. II. The Metabolic Influence of Copious Water Drinking with Meals, *J. Exper. Med.* **12**: 388, 1910.

Case 10 may be considered with this group, because, although the patient had advanced renal disease and at times had a negative sulphur balance, the serum protein values were at all times normal. It will be seen (table 1) that in him also the excretion of sulphur was diminished only slightly while he was on the diet low in sulphur. The nitrogen level of his diet was low, and as he was very sick he was unable to eat the diet as well as the other patients.

TABLE 1—*The Intake and Urinary Output of Sulphur and Nitrogen for Patients with Normal Serum Protein Values*

Case	Day	Sulphur, Gm		Nitrogen, Gm	
		Intake	Output	Intake	Output
10	1	38	63*	3.6	4.1*
	2	41	82	4.5	3.5
	3	44	39	4.3	3.3
	4	4	37	2.8	1.7
	5	3	78	1.8	4.4
	6	4	42	1.5	2.4
	7	40	46	4.5	2.5
	8	42	47	4.5	4.1
	9	46	52	4.5	4.2
17	1	84	64	9.7	8.4
	2	64	45	7.6	7.3
	3	72	47	8.5	7.4
	4	12	45	9.6	8.2
	5	12	37	8.5	7.7
	6	12	35	9.7	6.2
	7	81	42	9.6	7.5
	8	83	54	9.7	8.1
18	2	65	42	8.4	5.9
	3	64	41	8.8	5.4
	4	11	37	9.1	6.3
	5	15	33	9.6	6.6
	6	12	28	9.3	6.7
	7	62	37	8.2	6.8
	8	67	32	8.8	4.8

\* This figure was corrected from data on the excretion of creatinine.

Thus, in three patients with normal serum protein levels the response to gelatin feeding was a slight diminution in the urinary excretion of sulphur and a slight increase in the urinary excretion of nitrogen. These patients showed an average negative sulphur balance of 760 mg during the period of gelatin feeding (chart 1, upper columns).

The remaining patients studied had one factor in common in that they all showed some degree of depletion of serum proteins. All showed also evidence of glomerular lesions. With one exception, there was a strong tendency toward diminution of the excretion of sulphur in response to the diet low in sulphur. As the patients were all receiving the same amount of protein, about 60 Gm, it is proper to consider them



together (table 2) The nitrogen balance was close, with two patients exhibiting a strong tendency toward a negative balance in certain instances In two cases the experiments coincided with the disappearance of edema Only in case 14 was the albumin-globulin ratio reversed (table 3), although it was low in the other cases It is to be noted that in each patient there was a strongly positive sulphur balance before the

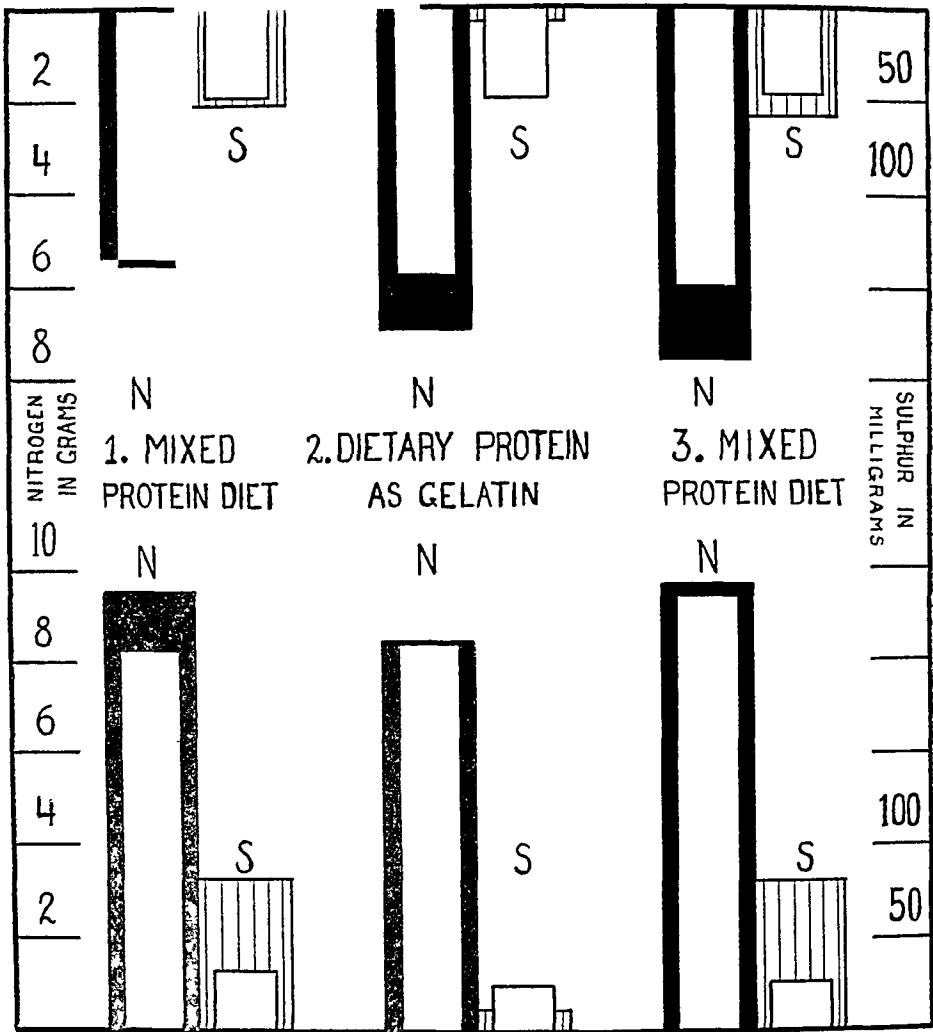


Chart 1—The upper columns show the average daily intake of nitrogen and sulphur and the urinary output for patients with normal serum protein values The lower columns show the daily intake of nitrogen and sulphur and the urinary output for patients with depleted serum protein values The solid or shaded columns represent the intake, the clear columns, the output The middle of each indicates the period of the gelatin diet Note the strongly positive sulphur balance shown in the lower columns and compare the slightly negative balance in this group during the period of gelatin feeding with the strongly negative balance shown in the upper columns

TABLE 2—*The Intake and Urinary Output of Sulphur and Nitrogen of Patients with Chronic Nephritis with Depleted Serum Protein Values*

Case	Day	Sulphur, Cg		Nitrogen, Gm	
		Intake	Output	Intake	Output
13	1	81	24	96	59
	2	80	20	95	51
	3	81	19	95	70
	4	13	33	96	78
	5	12	17	80	62
	6	12	14	73	52
	7	77	11	90	48
14	1	77	45	93	71
	2	82	37	96	118
	3	80	49	96	112
	4	10	14	56	54
	5	11	30	65	110
	6	12	17	78	62
	7	85	22	96	79
	8	77	39	95	96
	9	79	27	93	51
15	1	81	27	93	95
	2	81	43	85	100
	3	76	29	84	99
	4	10	32	94	105
	5	12	25	94	92
	6	14	27	96	108
	7	80	19	95	105
	8	77	33	84	120
	9	86	25	95	127
16	1	79	27*	96	83*
	2	81	24	93	82
	3	81	29	97	89
	4	12	26	91	100
	5	13	32	97	105
	6	13	32	97	99
	7	86	31	97	115
	8	81	27	97	89
	9	84	32	97	91

\* This figure was corrected from data on the excretion of creatinine

TABLE 3—*Laboratory Data During the Period of Study*

Case	Date	Blood Urea Nitrogen, Mg per 100 Cc	Blood Creatinine, Mg per 100 Cc	Blood Cholesterol, Mg per 100 Cc	Blood Sodium Chloride, Mg per 100 Cc	Excretion of Phenol sulphophthalein, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
10	10/10	32				5			
	10/14 to 11/7	27 to 50				10 to 15			
							76	50	26
13	12/19					52			
	12/22	13							
14	10/21					45			
15	11/13	20							
	11/15					20			
	12/4	20		382	483		56	39	17
16	3/2					78			
	3/6	10		411	450		46	21	25
	3/12	7		235	462	66	50	24	26
17	12/14	43	75	360			51	30	21
	12/17	52							
	12/22	43		310			48	30	18
18	10/30		50	355			46	25	20
	11/9	34							
	11/16	28	29	370			43	27	16
	11/18					10			

ingestion of the gelatin diet and that despite this the amount of sulphur excreted when little sulphur was given tended to be lower than in the patients with normal serum protein values. Whereas the first group of patients lost on the average, 0.76 Gm of sulphur during the gelatin feeding and the two normal controls lost 700 mg, the patients with low total serum protein values lost, on the average, only 400 mg. This can be shown also by comparing the nitrogen-sulphur ratios of the two groups (chart 2).

These experiments demonstrate no new fact but provide added evidence that the depletion of the serum proteins in Bright's disease is associated with the necessity of retention of sulphur in the organism. Further experiments are in progress to determine the fate of the retained sulphur.

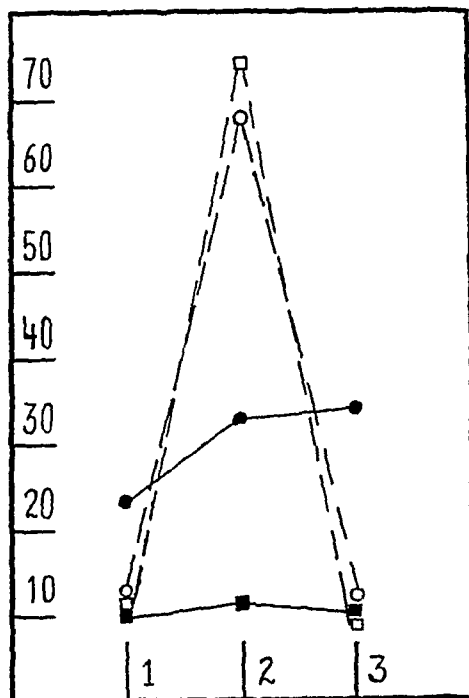


Chart 2—The nitrogen-sulphur ratios shown in chart 1. The broken lines connect the nitrogen-sulphur ratios of the intake, and the solid lines and solid figures, the ratios of the output. The squares represent the ratio in the urine of patients with normal serum protein values, and the circles, that of those with depleted serum protein values. Note the rise in the nitrogen-sulphur ratio in the patients with depleted serum protein values, indicating the effort to retain sulphur.

#### SUMMARY AND CONCLUSIONS

We have reported the effect of diets low in sulphur in seven patients. Three had normal serum protein values, and in four the values were low. The latter four had Bright's disease. The experiments showed that in patients with Bright's disease and low serum protein values the excre-

tion of sulphur tends to diminish to a greater extent than in patients with normal serum protein values when diets low in sulphur are given

#### REPORT OF CASES

CASE 10—A white man, aged 35, was admitted to the hospital on Sept 28, 1929, with a complaint of headache and vomiting. He was known to have had "kidney trouble" since 1908, when his feet and legs were swollen for a month. About a year prior to admission he noticed a feeling of ill health and an increase in the number of headaches. Vomiting became more severe and of longer duration until in the preceding four months it occurred almost constantly. Eight years before, he had an attack of so-called infantile paralysis, with almost complete bilateral facial paralysis and only slight symptoms in the arms and legs. The facial paralysis lasted for six months. Physical examination revealed a slightly enlarged heart and hemorrhagic retinitis. The blood pressure was 182 systolic and 110 diastolic. Only a trace of phenolsulphonphthalein was excreted. The blood count showed hemoglobin content, 30 per cent, and red cells, 3,200,000. The blood urea nitrogen was 52 mg per hundred cubic centimeters. The basal metabolic rate was minus 3 per cent. The patient improved symptomatically. Urinalysis revealed a low specific gravity, a slight trace of albumin and no formed elements of importance in the sediment. On October 10, the excretion of phenolsulphonphthalein was less than 5 per cent, the blood urea nitrogen was 32 mg, the hemoglobin content was 50 per cent, and the red blood cell count was 3,750,000. On October 14, the blood urea nitrogen was again 53 mg, and the urine showed a slight trace of albumin and many coarsely granular casts. The blood urea nitrogen varied from 50 to 27 mg, and the excretion of phenolsulphonphthalein ranged between 10 and 15 per cent. By October 31 red blood cells had appeared in the sediment, and these persisted. On November 7 the total blood protein was 7.6 per cent, the albumin, 5 per cent, and the globulin, 2.6 per cent. He was discharged, and was readmitted in January 1930. On April 22, 1930, he died of uremia, with the blood urea nitrogen 273 mg. At autopsy the right kidney was found to be contracted, weighing only 60 Gm, and the left kidney was almost entirely replaced by a cystic degeneration.

CASE 13—A white woman, aged 66, was admitted to the hospital on Dec 18, 1930, with a complaint of palpitation and fainting spells for fifteen years. She was observed in the outdoor department during this period, and constantly exhibited hypertension without evidence of renal disease. However, she had cardiac insufficiency and, for a number of years, auricular fibrillation. She was treated with digitalis, and her blood pressure was 250 systolic and 110 diastolic on admission. She was admitted to the hospital for rest in bed and for further study. On admission the basal metabolic rate was plus 25 per cent, the hemoglobin content was 83 per cent, and the red blood cell count was 5,500,000. The patient's heart was definitely enlarged and fibrillating, but there were no significant murmurs. Her stay in the hospital was uneventful, and she was discharged on Jan 17, 1931, improved, without much change in the blood pressure. The excretion of phenolsulphonphthalein on December 19 was 52 per cent, and on December 22 the blood urea nitrogen was 13 mg per hundred cubic centimeters. The urine showed the slightest possible trace of albumin on a few occasions and occasionally some hyaline casts. Subsequent to her discharge the patient followed the expected course and died on Oct 9, 1932, without giving evidence of renal failure.

CASE 14—A white woman, aged 65, was admitted to the hospital on Oct 20, 1930. She had been observed in our clinic since 1923, having had hypertension since that time. Her chief complaint was palpitation and dyspnea on exertion. On entrance the blood pressure was 230 systolic and 110 diastolic. There was moderate enlargement of the heart, but no evidence of congestive failure. The hemoglobin was 75 per cent, and the red blood cell count was 4,750,000. There was no evidence of retinal sclerosis, but moderate sclerosis of the peripheral arteries was present. The basal metabolic rate was plus 4 per cent. On October 21 the excretion of phenolsulphonphthalein was 45 per cent. During her stay in the hospital, her blood pressure gradually fell to 180 systolic and 90 diastolic. At times the urine showed a few red cells and rare finely granular casts, and occasionally there was the slightest possible trace of albumin. The patient had no edema and was discharged improved on Dec 16, 1930.

CASE 15—A white married woman, aged 58, was admitted to the hospital on Nov 12, 1930. In 1917 albuminuria and a few casts appeared in the urine following lobar pneumonia and an abscess of the lung. For the next ten years her renal function remained good. The excretion of phenolsulphonphthalein was above 40 per cent on various occasions. In 1928 she began to complain of dizziness and headache. She then showed hypertension, the pressure being 215 systolic and 110 diastolic. The heart was slightly enlarged, and the urine showed a trace of albumin and numerous casts. In April 1929, she had an acute attack of pyelitis, with fever and chills. Her blood pressure fell to 145 systolic and 64 diastolic during this period, and the blood urea nitrogen rose to 39 mg per hundred cubic centimeters during the acute illness, but fell to 17 mg as she improved. There were no casts in the urine, but there was some edema. During the entire period she had mild diabetes, which was readily controlled by diet. In November 1929 she returned to the hospital. The blood pressure was 204 systolic and 98 diastolic, the blood urea nitrogen was 86 mg, the blood sugar was 149 mg, and the excretion of phenolsulphonphthalein was 25 per cent. After that, the urine always showed a large trace of albumin and a slight trace of sugar. The blood pressure remained around 240 systolic and 120 diastolic. Six weeks before the last admission she complained of drowsiness, this was observed at the time she was admitted. On admission the blood pressure was 220 systolic and 129 diastolic, and the blood sugar was 194 mg. Her heart was enlarged, and there was slight pitting edema. The hemoglobin content was 60 per cent, the red blood cell count, 3,800,000, the blood urea nitrogen, 20 mg per hundred cubic centimeters, and the excretion of phenolsulphonphthalein, 20 per cent. She improved rapidly, and there was no demonstrable edema during the period of the experimental study. Digitalis was given throughout her stay in the hospital. During the entire period the specific gravity of the urine varied between 1.007 and 1.014, and the urine constantly showed a trace of albumin, the slightest possible trace of sugar and occasional casts. The patient was discharged on Dec 9, 1930, much improved.

CASE 16—A white woman, aged 18, was admitted to the hospital on Feb 7, 1931, with a complaint of edema of the ankles of six weeks' duration following an infection of the upper respiratory tract. Her history revealed that she noticed a slight swelling of each ankle one year before admission, but that she had felt well. On admission, physical examination revealed a white spot in one retina and one small, old hemorrhage in the other. There was moderate enlargement of the thyroid isthmus, and the blood pressure was 132 systolic and 82 diastolic. There

was distinct pitting edema of the legs which disappeared over night. She was essentially symptom-free throughout her stay. Her basal metabolic rate was plus 5 per cent. The hemoglobin content was 80 per cent, and the red blood cell count was 4,000,000. On March 10 there was slight pitting edema which soon disappeared. The excretion of phenolsulphonphthalein was between 66 and 80 per cent, the blood urea nitrogen varied from 7 to 14 mg per hundred cubic centimeters, and the blood cholesterol was 416 mg per hundred cubic centimeters. The total blood protein was 4.8 per cent, the albumin was 2 per cent and the globulin, 2.8 per cent. The urine showed from a slight trace to a trace of albumin throughout her stay, and, rarely, red blood cells and occasional casts. The middle of March the blood protein content began to rise. By April 16 the blood protein value was normal and the cholesterol concentration had fallen. She was discharged, much improved, May 3.

CASE 17—A white man, aged 24, was admitted to the hospital on Dec 10, 1931, complaining of blurred vision and headache. His history showed that in 1927 he first noticed generalized edema, at that time a large amount of albumin and some casts were found in the urine, but there was no hypertension. He was given a diet high in protein and was considered to have passed through the nephrosis syndrome. He was followed up in the outdoor department after his discharge. He felt fairly well for a few months, although he continued to have some edema. Headache and dimness of vision persisted, and there gradually developed hypertension, which on the last admission was 170 systolic and 110 diastolic. On this admission there was secondary anemia, the red blood cell count being 3,900,000, the blood urea nitrogen was 51 mg, and the excretion of phenolsulphonphthalein, 2 per cent. He had no edema and had had none for a year. There were marked retinal arteriosclerosis and some cardiac enlargement. The urine showed a large amount of albumin, an occasional granular and hyaline cast and a good many red cells. He complained of blurred vision and headache, weakness and occasional twitching. The blood protein value was slightly lowered, the total protein being 5.1 per cent, the albumin, 3 per cent, the globulin, 2.1 per cent, the cholesterol, 360 mg per hundred cubic centimeters, and the creatinine, 7.5 mg per hundred cubic centimeters. By January 4, the blood creatinine had fallen to 3 mg, but the excretion of phenolsulphonphthalein amounted to only a trace. The blood urea nitrogen remained at about the same level, and symptomatically he was relieved. He was discharged on Jan 17, 1932.

CASE 18—A white woman, aged 20, was admitted to the hospital on Oct 29, 1931, complaining of edema. Her history showed scarlet fever in infancy and diphtheria at the age of 4 years. In 1927 she sprained an ankle and both ankles, the legs and the face began to swell. At that time she was admitted to the outdoor department, where she has been followed since. Her blood pressure at that time was 147 systolic and 90 diastolic, and there was a large amount of albumin in the urine as well as a moderate number of casts. She had secondary anemia, the specific gravity of the urine was 1.010, and the reaction was constantly alkaline. Increasing hypertrophy of the heart was noticed, the blood urea nitrogen was 27 mg, and the excretion of phenolsulphonphthalein was 25 per cent and later 17 per cent. She was given a salt-free diet low in protein and remained fairly well until September 1931, when a cold caused an increase in the edema. Headache became a troublesome symptom, and the blood pressure rose to 174

systolic and 100 diastolic. On admission to the hospital her blood pressure was 190 systolic and 110 diastolic, the red blood cell count was 2,950,000, the hemoglobin count, 55 per cent, and the blood urea nitrogen, 33 mg. The excretion of phenolsulphonphthalein had fallen to 10 per cent on admission. The total protein was 4.6 per cent, the albumin, 2.5 per cent, the globulin, 2 per cent, the creatinine, 5 mg. and the cholesterol, 355 mg. She was given a diet high in protein, but by November 3 there was no demonstrable edema, and by November 16 the blood creatinine had fallen to 2.9 mg. On November 13, there was again definite edema, without a change in the laboratory observations to account for it. The urine, throughout, showed from a trace to a large trace of albumin, a few casts and a few red cells. She was discharged on November 27 still slightly edematous. She died in June 1932.

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# CARDIOVASCULAR STATUS OF DIABETIC PATIENTS AFTER THE FOURTH DECADE OF LIFE

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An analysis of the cardiovascular status of the diabetic patient involves chiefly a study of the interrelationship of arteriosclerosis and diabetes. One hundred and twenty cases in patients above the age of 39 have been observed with this in view. The data presented here deal with the incidence of the important cardiovascular variants, and with their relation to age and sex and to the severity and duration of diabetes. To these are added some observations on the clinical types of arteriosclerosis in diabetic patients and on the significance of retinitis and abnormalities of the electrocardiogram. The primary data are tabulated in table 1 and summarized in table 2. The relation to sex is shown in table 3 and to age in table 4.

## CARDIOVASCULAR VARIANTS

*Cardiac Enlargement*—The heart in nondiabetic arteriosclerotic patients is as often small as large. In the autopsy material analyzed by Cabot,<sup>1</sup> 64 per cent of all patients (951) with arteriosclerosis<sup>2</sup> had large hearts, but excluding patients with pericarditis, valvular lesions, nephritis and some other unspecified lesions the incidence of cardiac hypertrophy was only 46 per cent, and excluding the first three groups only it was 39 per cent. The striking feature of these observations is the frequent absence of cardiac enlargement in patients with arteriosclerosis. Attention has heretofore been directed to the relation of arteriosclerosis to cardiac hypertrophy. The reverse of the picture is equally important. In general, it may be said that somewhat more than half of the patients with uncomplicated arteriosclerosis and somewhat less than half of those with complicated arteriosclerosis have small hearts at death, the percentage varying with the complicating factor and other determining influences, such as age at death and sex.

In this series of diabetic patients, which includes some with potential as well as those with manifest arteriosclerosis, the percentage of inci-

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From the medical service and the outpatient department of the Sydenham Hospital

1 Cabot, Richard C. Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, pp. 417 and 423.

2 These probably include some diabetic patients.



TABLE 1—Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39\*

1	2	3	4	5	6	7	8	9	10	11	12
Case No.	Age	Sex	Blood Pressure	Size of Heart	Aorta	Fundus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
1	53	F	0 to +	+		+	(1931) T <sub>3</sub> flat, low voltage QRS (1933) T <sub>3</sub> inverted, premature auricular contractions, QRS normal, LAD	++	++	None	Tumenculosis, cholelithiasis (?)
2	56	F	+	+	+	+	T <sub>3</sub> flat, T <sub>3</sub> inverted, LAD	++	+	Dyspnea, palpitation	None
3	72	M	+	+			T <sub>1</sub> diphasic, LAD	++	++	Dyspnea, slight decompensation	Transient loss of vision
4	51	M	0	0			T <sub>3</sub> flat, low voltage QRS	++	++	None	None
5	64	F	+ to 0	+	+	++	T <sub>3</sub> inverted	++	++	Dyspnea, palpitation	Bronchopneumonia
6	63	F	0		+	+	T <sub>1</sub> flat, T <sub>2</sub> inverted, LAD	+++	++	Slight dyspnea, palpitation	Cataract
7	46	F	0	0	0	0	T <sub>3</sub> flat, LAD	++	++	Slight dyspnea	None
8	61	F	+ to 0	+	++	++	Deep Q <sub>3</sub> , LAD	+++	+	None	Fever of unknown origin
9	45	M	0	0	+	0	T <sub>1</sub> flat, low voltage QRS, LAD	+	+	None	Osteomyelitis of foot
10	62	F	+	0	++	+	5 records in six months LAD	++	++	Dyspnea, palpitation, edema of ankles	Cerebral thrombosis, hemiplegia
11	65	F	+	0	++	0	(1932) T <sub>3</sub> flat, normal QRS LAD	++	+	None	Cholecystitis
12	62	M	0	0	++	+	(1933) T <sub>1</sub> flat, LAD	+	+	None	Infection of finger
13	61	M	0	+	++	+	T <sub>3</sub> inverted, LAD	++	+	None	Cholecystitis, syphilis
14	60	M	+	++	+++	+	Prolonged auriculoventricular conduction, LAD	+++	+	Dyspnea	None
15	85	M	+	+	++	++	LAD	+	+	Slight dyspnea on exertion	Cataracts
16	64	F	+ to 0	0	0	++	T <sub>3</sub> flat	++	+	None	None
17	52	F	+	+	+	+	T <sub>3</sub> inverted, LAD	++	+	Palpitation, dyspnea	None
18	58	F	+	++	+	+	T <sub>2</sub> inverted, LAD	+	+	Substernal pain	None
19	75	F	+	+	++	0	T <sub>3</sub> inverted, LAD	++	+	Dyspnea, palpitation, decompensation	Carcinoma of bladder
20	46	M	0	+			T <sub>3</sub> inverted, LAD	++	+	None	None
21	59	F	+	+	0	++	(1929) T <sub>1</sub> inverted (1930) T <sub>1</sub> flat (1931) Normal	+++	++	None	Infection of upper respiratory tract
22	57	F	0 to +			+	T <sub>3</sub> inverted LAD	+	+	None	None
23	76	M	0			++	Auricular fibrillation intravenous block, T <sub>1</sub> inverted LAD	++	+	Precordial pain, dyspnea, decompensation	None
24	68	F	0	+	++	+	(1931) T <sub>3</sub> inverted LAD (1933) T <sub>3</sub> inverted, LAD	++	+	Dyspnea on exertion	Carbuncle of scalp, purpura simplex

25	50	F	+	0	0	+	0	T <sub>2</sub> flat, T <sub>3</sub> inverted, LAD	+	+	+	+	None
26	42	F	0	0	+	0	0	T <sub>2</sub> inverted, low voltage QRS, LAD	+	+	+	+	None
27	58	F	0	+	+	0	+	T <sub>2</sub> inverted, premature auricular and nodal contractions, LAD	+	+	+	+	None
28	48	F	0	0	0	+	+	(1933) T <sub>1,2,3</sub> flat, LAD	+	+	+	+	None
29	49	F	+	+	+	+	+	(1933) T <sub>2</sub> inverted, LAD	+	+	+	+	None
30	60	F	+	+	+	+	+	T <sub>2</sub> inverted, LAD	+	+	+	+	Psoriasis
31	68	F	+	to 0	0	+	+	T <sub>2</sub> inverted, LAD	+	+	+	+	Partial loss of vision
32	69	M	+	+	+	+	+	(1929) LAD	+	+	+	+	Cerebral arteriosclerosis, senile psychosis
33	53	F	0	0	+	+	+	(1930) LAD	+	+	+	+	None
34	60	F	0	+	0	+	+	(1932) T <sub>1</sub> diphasic, LAD	+	+	+	+	Infection of foot
35	48	F	0	0	0	+	+	T <sub>1</sub> inverted, T <sub>2</sub> flat, LAD	+	+	+	+	None
36	69	M	0	0	0	+	+	LAD	+	+	+	+	Infection of hand and buttock
37	49	F	+	to 0	+	+	+	T <sub>2</sub> inverted, LAD	+	+	+	+	Hallux valgus
38	43	F	+	+	0	+	+	T <sub>2</sub> inverted, LAD	+	+	+	+	None
39	49	F	+	+	0	+	+	T <sub>2</sub> flat, low voltage QRS, LAD	+	+	+	+	None
40	42	M	0	0	0	+	+	T <sub>2</sub> inverted, LAD	+	+	+	+	None
41	45	F	+	to 0	+	+	+	Low voltage QRS	+	+	+	+	None
42	44	F	0	0	0	+	+		+	+	+	+	Palpitation

\* Column 2 Age is recorded as of the last observation

Column 4 0 indicates a blood pressure up to 150 mm of mercury systolic or 100 mm diastolic, + a pressure of over 150 mm systolic or 100 mm diastolic

Column 5 0 indicates a normal or small heart +, a slight or questionable enlargement, ++, a moderate enlargement, and +++ a more than moderate enlargement

Column 6 0 indicates a normal aorta, +, increased density, ++, dilatation, increased density and calcification, and +++ thin arteries, spasm and retinal degeneration, and +++ thin arteries, spasm and calcification of a greater degree with elongation and coiling

Column 7 0 indicates a normal fundus, +, thin arteries or spasm, ++, thin arteries, spasm and retinal degeneration, and +++ LAD indicates left axis hemorrhages

Column 8 Not graded in this table All significant or probably significant abnormalities of the electrocardiogram are included

Column 9 Duration of diabetes is recorded as of the last observation + indicates a duration of less than one year, ++, of from one to four years, +++, of from four to nine years, and ++++, of ten years or over

Column 10 Severity of diabetes is graded +, ++ and +++ The grading is based in each case on comparatively loosely applied criteria These were (1) the ease of difficulty with which control was established and maintained, (2) the level of carbohydrate tolerance, and (3) the frequency of infection Control was indicated by sugar free urine and a blood sugar before breakfast or over with maintenance of caloric intake, no attempts were made to reduce the blood sugar, unless it exceeded in all specimens on diets of 100 Gm of carbohydrate tolerance with metabolic control were +, indicates 100 Gm or higher of carbohydrate without insulin and with 200 mg per 100 cc The criteria of carbohydrate tolerance without insulin or 100 Gm of carbohydrate with less than 25 units of insulin daily, moderate blood sugar levels, ++, less than 100 Gm of carbohydrate without insulin or 100 Gm of carbohydrate with less than 25 units of insulin daily, +++, higher insulin requirements, irregular insulin distribution or irregular blood sugar curves The estimates from the tolerance level were modified by the factors of the ease of control and the appearance of complicating infections Only grade + cases were considered mild

Columns 11 and 12 Cardiac symptoms and complications include only those during the period of observation, or immediately preceding it The period of observation for my cases varied from less than one month to five years and for those of others, up to ten years

TABLE 1—Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39—Continued

Case	Age	Sex	Blood Pressure	Size of Heart	Aorta	Fundus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
1	2	3	4	5	6	7	8	9	10	11	12
1	41	F	0 to +	0	++	++	Normal (1931) T <sub>12</sub> inverted (1932) T <sub>12</sub> inverted deeply	+++	+	None	Cholelithiasis, anthrax
2	41	F	+	+	+	+		+++	+	Substernal pressure, edema, decompensation, death	None
3	41	F	0	0	++	0	Low voltage QRS	+	++	None	None
4	41	F	+	0	++	0	T <sub>123</sub> diphasic (digitalis)	+++	+	Dyspnea, palpitation	None
5	41	F	0	0	++	++	T <sub>3</sub> flat, low voltage QRS	+++	+	None	Pulmonary tuberculosis
6	41	F	0	0	++	+	LAD	+++	+	Dyspnea on exertion	None
7	41	F	0	0	0	+	LAD	+++	+	None	None
8	41	M	0	0	0	0	Peaked T wave	+++	+	Dyspnea	Chronic bronchitis, bronchiectasis
9	41	M	0 to +	0	0	0	T <sub>12</sub> inverted, low voltage QRS, LAD	+++	+	Substernal compression, dyspnea	Infection of arm
10	41	F	0 to +	+	0	0	T <sub>3</sub> flat, LAD	+	+	None	Asthma
11	41	F	+	0	0	0	LAD	+	+	Palpitation	Fracture of toe
12	41	F	+	0	++	+	Slurred QRS, LAD	+	+	None	Healed mitral stenosis
13	41	F	0	+	++	+		+	+	None	None
14	41	F	0	+	0	0	(1930) LAD	+	+	None	Infection of foot
15	41	F	+	0	0	0	(1931) Transient auricular fibrillation, LAD	+	+	None	Appendicitis
16	41	F	+	0	0	+	T <sub>3</sub> inverted, LAD	+++	+	Substernal compression, dyspnea, palpitation	None
17	41	M	0	0	+	0		++	+	None	None
18	41	M	0	0	+	0	T <sub>3</sub> flat, LAD	++	+	None	Syphilis
19	41	F	0	0	+	+	Interventricular block, wide, low voltage QRS, T waves upright	+++	+	Palpitation, precordial and substernal pain	Cerebral concussion
20	41	F	+	+	++	+	Normal	+++	+	None	Fractures of clavicle and three ribs
21	41	F	+	+	++	+	T <sub>2</sub> flat, T <sub>3</sub> inverted, LAD	+++	+	Precordial pain, dyspnea	None
22	41	F	+	+	++	+	LAD	+++	+	None	Furunculosis
23	41	F	+	+	++	+	T <sub>2</sub> flat, T <sub>3</sub> inverted	++	+	None	Psoriasis, cataract
24	41	M	0	0	0	0		++	+	None	Active pulmonary tuberculosis
25	41	F	+	0	++	+	Normal	+++	+	None	None
26	41	F	+	0	++	+	T <sub>3</sub> inverted LAD	+++	+	Dyspnea	Pyelonephritis, uremia (fatal)
27	41	F	+	+	+	+	T <sub>3</sub> inverted	++	+	Dyspnea	Menorrhagia ulcer of leg
28	41	F	+	+	0	0	(1928, 1930 and 1932) T <sub>3</sub> flat (1930 and 1931) T <sub>3</sub> inverted	+++	+	None	None
29	41	F	0	0	0	+	LAD	+++	+	Dyspnea, substernal pain	None

[illegible]

TABLE 1—Summary of Observations on 120 Cases of Diabetes Mellitus in Persons Aged Over 39 \*—Continued

1	2	3	4	5	6	7	8	9	10	11	12
Case	Age	Sex	Blood Pressure	Size of Heart	Aorta	I undus	Electrocardiogram	Duration of Diabetes	Severity of Diabetes	Cardiac Symptoms	Complications
98	45	F	0	0	0	0	T <sub>3</sub> variable	+++	++	None	Cholecystitis, hysteria
99	70	M	1	0	0	+	LAD	+	+	None	Intermittent claudication
100	53	F	+	+	1	1	T <sub>3</sub> Inverted, LAD	1	+	Dyspnea	None
101	60	F	0	0	0	0	(1929) LAD	+++	+	None	Hysteria
102	60	M	0	0	0	0	(1932) T <sub>3</sub> inverted, LAD	+	+	None	None
103	72	F	+	0	0	+	T <sub>3</sub> flat, LAD	1	+	None	None
104	67	F	1	0	1	+	T <sub>1</sub> diphasic, low voltage QRS	+++	+	Dyspnea, palpitation, decompensation	Gastritis
					1	+	(1924) Deep Q <sub>3</sub> , LAD	+++	++	None	None
					1	+	(1930) T <sub>123</sub> inverted, wide QRS	++	+	Dyspnea, palpitation (terminal)	None
105	52	F	0	+	+	+	T <sub>3</sub> inverted, LAD	+	++	Dyspnea, palpitation precordial pain	None
106	62	F	+	0	+	+	LAD	++	+	None	None
107	53	F	0	0	1	+	T <sub>1</sub> diphasic, low voltage QRS	+++	+	None	Gonorrhea
108	42	F	0	0	+		Normal	++	++	Dyspnea, palpitation, precordial pain	Cervical lymphadenitis
109	56	F	0	+	+	0	(1929 and 1933) T <sub>3</sub> flat, LAD	++	+	None	Fistula in ano, furuncles, chronic cystic mastitis
110	75	F	+	0	+	+	LAD	++	+	None	Arthritis
111	69	F	+	++	++		Intraventricular block, delayed auriculoventricular conduction, T <sub>123</sub> inverted	++	+	None	Kerato conjunctivitis (traumatic), cataracts
112	10	M	0	0	+	++	(1931) T <sub>3</sub> inverted	++	+	None	Pulmonary tuberculosis
113	47	M	0	+	+		(1932) T <sub>2</sub> diphasic, T <sub>3</sub> inverted	+	+	None	None
114	68	F	1	0	+	+	T <sub>3</sub> flat	++	+	Precordial pain, dyspnea, palpitation	None
115	44	F	0	+	+	+	T <sub>3</sub> inverted, LAD	++	+	None	Pyloritis, fibroid uterus, furunculosis
116	64	F	+	+	0	+	T <sub>3</sub> inverted, LAD	++	+	Substernal pain, palpitation, decompensation	Fracture of wrist
			+	+	+	+	(1929-1930) Normal	+	+	Dyspnea, palpitation, precordial pain	Nephrolithiasis, cholecystitis, fibroid uterus
117	41	F	0	+	+	+	(1931) T <sub>1</sub> diphasic, LAD	+	+	None	None
			0	+	+	+	(1932) T <sub>1</sub> flat, LAD	+	+	None	None
			0	+	+	+	(1933) T <sub>1</sub> diphasic, LAD	+	+	None	None
			0	+	+	+	(1930) T <sub>1</sub> diphasic, LAD	+	+	None	None
			0	+	+	+	(1931) T <sub>1</sub> inverted, LAD	+	+	None	None
			0	+	+	+	(1932) T <sub>1</sub> inverted, LAD	+	+	None	None
118	42	F	0	0	0	1	T <sub>3</sub> inverted, deep Q <sub>3</sub> IAD	+	+	Dyspnea, palpitation, precordial pain	Cerebral thrombosis (fatal)
119	61	F	1	+	1	1	T <sub>1</sub> inverted, LAD	++	+	None	None
120	47	F	1	+	1	1	(Mar 1931) T <sub>3</sub> inverted LAD (Nov 1931) T <sub>2</sub> diphasic, T <sub>3</sub> inverted LAD (1932) T <sub>1</sub> flat T <sub>23</sub> inverted	+	+	Substernal pain, dyspnea, palpitation	None

dence of cardiac enlargement was similar to that in Cabot's series, composed entirely of patients with manifest arteriosclerosis. Slightly more than one half (53 per cent) had small or normal-sized hearts, and slightly less than one half (47 per cent) had enlarged hearts, but in only 18 per cent was the enlargement more than slight. Cardiac enlargement was not much more frequent in these diabetic patients than in those with otherwise uncomplicated arteriosclerosis, and considerably less frequent than in those with otherwise complicated arteriosclerosis. In less than one fifth of diabetic patients past the fourth decade of life is there any considerable hypertrophy.

Cardiac enlargement in diabetes is twice as frequent in females as in males (table 3) if a slight degree of enlargement is included, and only slightly more frequent if the grade 1 type of enlargement is excluded.

TABLE 2—*Percentage Incidence of Cardiovascular Abnormalities*

	Incidence	Total Cases Analyzed
Atherosclerosis of aorta (grades 1, 2 and 3)	75%	83
Atherosclerosis of aorta (grades 2 and 3)	60%	83
Retinal arteriosclerosis	69%	101
Retinitis	28%	101
Hypertension (transient and permanent)	56%	119
Hypertension (permanent)	38%	119
Enlarged heart (grades 1, 2 and 3) (including slight enlargement)	47%	101
Enlarged heart (grades 2 and 3) (excluding slight enlargement)	18%	101
Abnormalities of electrocardiogram (abnormalities of T <sub>1</sub> or T <sub>2</sub> and conduction defects)	35%	117
Abnormalities of electrocardiogram (including also low voltage QRS and deep Qs)	45%	117
Left axis deviation	73%	117
Cardiac symptoms (including slight and variable symptoms and pain of all types)	46%	120
Cardiac decompensation (including two cases with angina pectoris)	8%	120
Cardiac pain	19%	120
Angina pectoris	9%	120

In the fifth decade of life, cardiac enlargement is less frequent than the average for all ages together. The percentage rises in the sixth decade and then drops sharply in the seventh and later decades. A perusal of table 4 will show that the precipitate fall in the incidence of cardiac enlargement after the sixth decade is in sharp contrast to the steady increase with age in the incidence of most cardiovascular abnormalities. It may be attributed to one or more of three possible factors: (1) the effect of a debilitating disease, (2) premature death of patients with enlarged hearts in the sixth decade of life and (3) the appearance of new cases of diabetes without cardiac enlargement at advanced ages (Allbutt's decrescent arteriosclerosis). Of these three factors, the first may be considered of negligible importance under the present conditions of metabolic control, the second seems to me to be of less importance than the third, the last two together adequately explain this unusual decrease.

The results of the autopsy studies of Nathanson<sup>3</sup> agree with these clinical observations. In 98 cases 86 per cent of which were in patients beyond the fourth decade of life, the heart was enlarged to more than 450 Gm in 17 per cent. Including enlargements over 400 Gm, the incidence of cardiac hypertrophy was 41 per cent. The close agreement with the percentages shown in table 2 is partly accidental, since the distributions according to age and sex in his series are different than in this. Warren<sup>4</sup> reported that only 31 per cent of 283 diabetic patients showed enlargement of the heart to above 350 Gm, but his cases included those of all ages.

TABLE 3—Percentage Incidence of Cardiovascular Abnormalities by Sex

	Male	Female
Retinal arteriosclerosis	47%	74%
Retinitis	21%	29%
Hypertension (transient and permanent)	19%	67%
Hypertension (permanent)	19%	43%
Atherosclerosis of aorta (grades 2 and 3)	58%	61%
Enlarged heart (grades 1, 2 and 3)	26%	53%
Enlarged heart (grades 2 and 3)	13%	19%
Abnormalities of electrocardiogram (abnormalities of T <sub>1</sub> or T <sub>2</sub> and conduction defects)	31%	36%

TABLE 4—Percentage Incidence of Cardiovascular Abnormalities by Age

	40 to 49 Years	50 to 59 Years	60 Years and Over
Retinal arteriosclerosis	47%	82%	77%
Retinitis	13%	34%	33%
Hypertension (transient and permanent)	46%	51%	67%
Hypertension (permanent)	30%	36%	45%
Atherosclerosis of aorta (grades 2 and 3)	31%	63%	79%
Enlarged heart (grades 1, 2 and 3)	39%	60%	44%
Enlarged heart (grades 2 and 3)	9%	28%	19%
Abnormal electrocardiogram (abnormalities of T <sub>1</sub> or T <sub>2</sub> and conduction defects)	19%	39%	44%

The clinical and autopsy data, disregarding the differences arising from sex and age distribution, are adequate to prove the relative infrequency of cardiac enlargement in diabetic cases in the arteriosclerotic zone. The published data from autopsies are not sufficient to confirm the sex and age differences which are indicated in tables 3 and 4.

*Hypertension*—Major<sup>5</sup> has shown that at comparably advanced ages the frequency of hypertension above 150 mm of mercury is higher in diabetic patients than in otherwise normal controls, or than

3 Nathanson, M. H. Coronary Disease in One Hundred Autopsied Diabetics, *Am J M Sc* **183** 495, 1932.

4 Warren, S. The Pathology of Diabetes, Philadelphia, Lea & Febiger, 1930, p 148.

5 Major, S. G. Blood Pressure in Diabetes Mellitus *Arch Int Med* **44** 797 (Dec) 1929.

in the general hospital or clinic population. His percentages and also Kramer's<sup>6</sup> were somewhat lower than those shown in table 4. Both these, as well as other, investigators have demonstrated the increasing incidence of hypertension with advancing age. In the present series the rise was uninterrupted from 46 per cent in the fifth decade to 67 per cent in the seventh and later decades, but the series included many cases of transient hypertension. Excluding the latter, the incidence increased from 30 per cent in the fifth to 45 per cent in the seventh and later decades, which conforms more closely to that in Major's larger series and also to Sherril's<sup>7</sup> results.

Permanent hypertension in association with diabetes is over twice as frequent among females as among males. Including transient hypertension, it is three and one-half times as frequent.

*Arteriosclerosis of the Aorta and Retinal Arteries*—Arteriosclerosis in either the aorta or the retinal arteries was present in 89 per cent of these patients, in both the aorta and the retinal arteries, in 51 per cent. The high incidence of vascular disease in diabetic patients past the fourth decade, now widely recognized, is indicated in table 2. It occurred in the aorta in 75 per cent of the patients, with dilatation in 60 per cent. It was present in the retina in 69 per cent. Involvement of each of these organs showed a greater incidence in females than in males, but the differences are less marked in the case of aortic arteriosclerosis. As might be expected, the percentages increase with age, the sharpest increase being between the fifth and the sixth decade. In the case of aortic arteriosclerosis, the increase continues into the seventh decade, for retinal arteriosclerosis, it diminishes slightly.

*Retinitis*—The retinitis of diabetes is the arteriosclerotic retinitis first described as such by Moore<sup>8</sup> and distinguished by him from the retinitis of nephritis. Some<sup>9</sup> still dispute this view, chiefly because of the failure to distinguish arteriosclerotic nephritides from the other types. In the diabetes of childhood and adolescence, retinitis is rare,<sup>10</sup> and when found it is usually in the very severe or badly controlled cases. The incidence increases with age from a relatively low value (13 per cent) in the fifth decade (table 3) to 34 per cent in the sixth. Follow-

6 Kramer, D. W. Hypertension and Diabetes, *Am J M Sc* **176** 23, 1928.

7 Sherril, J. W. Cardiovascular Disease in Diabetes Mellitus, *California & West Med* **38** 73, **39** 17, 1933.

8 Moore, R. F. The Retinitis of Arteriosclerosis and Its Relation to Renal Retinitis and to Cerebral Vascular Disease, *Quart J Med* **10** 29, 1917.

9 Bessiere, E. Existe-t-il une rétinite diabétique en l'absence d'altérations rénales? *Arch d'ophth* **49** 219, 1932.

10 White, Priscilla. Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, pp 193 and 217. Wagener, H. P., and Wilder, R. M. The Retinitis of Diabetes Mellitus, *J A M A* **76** 515 (Feb 19) 1921.



ing this, there is no further increase. Females were found to have retinitis only slightly more frequently than males. Every patient with retinitis had also retinal arteriosclerosis, inevitably, in view of its arteriosclerotic origin. Spalding and Curtis<sup>11</sup> found a similar association. The total incidence of retinitis in their patients was lower than that (28 per cent) found in this series, but they included persons below the age of 40. It should be noted that after the fourth decade retinitis develops in 4 of every 10 patients with retinal arteriosclerosis.

*Abnormalities of the Electrocardiogram*—Abnormalities of the T waves in leads I and II occurred in 39 out of 117 patients, an incidence of 33 per cent. Of these, 9 also had a low voltage QRS complex, 3 had intraventricular block, 1 with delayed auriculoventricular conduction time and another with auricular fibrillation, 4 had a widened QRS complex and 1 of these, a deep  $Q_s$  wave. Of the 78 patients without abnormalities of the T wave, 1 had delayed auriculoventricular conduction time, 1, intraventricular block, 1, transient auricular fibrillation, 7, a low voltage QRS complex, and 4, a deep  $Q_s$  wave. There were no patients with right axis deviation. Left axis deviation was present in 85 patients (73 per cent). Of the patients with otherwise normal T waves, 51 (65 per cent) had a flattened or inverted  $T_s$  wave.

If one includes as significant only abnormalities of the T wave in leads I and II and defects in conduction (excluding transient auricular fibrillation), there were 41 (35 per cent) grossly abnormal records. Including all the abnormalities mentioned there were 53 (45 per cent). Hepburn and Graham<sup>12</sup> found an incidence of 45.5 per cent, including, however, patients of all ages and with minor electrocardiographic abnormalities. They also demonstrated the increased incidence with advancing age which is shown in table 4. The sharpest increase here was between the fifth and the sixth decade. The percentage of incidence was also slightly higher in females than in males (table 3).

*Cardiac Symptoms, Cardiovascular Sequelae and Complications*—Cardiac symptoms were absent in 65 patients (54 per cent). There were 10 patients (8 per cent) with cardiac decompensation, of whom 2 died, 23 patients (19 per cent) had cardiac pain, but of these only 11 (9 per cent) were considered to have angina pectoris. One of the latter died as a result of cerebrovascular insult. Most of the others with cardiac symptoms had slight evidence of impairment of cardiac reserve. Besides the patient who died there were 2 (2.5 per cent) who had cere-

11 Spalding, E. M., and Curtis, W. S. Retinitis and Other Changes in the Eyes of Diabetics, Boston M. & S. J. **197** 165, 1927.

12 Hepburn, J., and Graham, D. An Electrocardiographic Study on One Hundred and Twenty-Three Cases of Diabetes Mellitus, Tr. A. Am. Physicians **43** 86, 1928.

bral thrombosis and hemiplegia and 1 with senile psychosis and cerebral endarteritis. There was 1 patient with intermittent claudication, but in no instance did gangrene of the lower extremities appear. As in the experience of others, the most frequent complication was infection (abscesses, furuncles and osteomyelitis), which occurred in 16 cases (13.3 per cent). In 5 cases there was infection of the feet. Other complications were cholecystitis (9 cases), pulmonary tuberculosis (4), cataract (8), arthritis (4), syphilis (3) and pyelonephritis (2). Miscellaneous complications included glaucoma, psoriasis, xanthoma, fractures and hysteria.

#### RELATION OF FACTORS TO DIABETES

*Age and Sex Distribution*—Patients above the age of 39 now represent roughly about nine tenths of the total diabetic population.<sup>13</sup> Before the era of insulin the percentage of patients with diabetes past the fourth decade was already rising,<sup>14</sup> owing to the combined factors of the aging of the general population and the preponderant incidence of diabetes with late onset (two thirds of all the cases begin after the age of 39, and three fourths of those of ten years' duration).<sup>15</sup> The diabetic population may now be said to be aging for these reasons as well as because of the demonstrable lengthening of the life span of diabetic patients in the Banting era, in which an increasing number are brought into the later decades of life.<sup>16</sup> This series represents, therefore, a small cross-section of a large part of the typical diabetic population, considered from the standpoint of age distribution. By decades the distribution is as follows: in the fifth, 37 patients, in the sixth, 33, in the seventh, 41, and in the eighth and later ones, 9.

The sex distribution in these cases is somewhat atypical. There were 27 males and 93 females (77.5 per cent), that is, the distribution is heavily weighted for females. In other series of diabetic cases, the excess of females has generally been much smaller, and in some the number of cases has been about equally divided between males and

13 Joslin, E. P., Dublin, L. I., and Marks, H. H. *Studies in Diabetes Mellitus. Its Incidence and the Factors Underlying Its Variations*, Am J M Sc **187** 433, 1934.

14 Emerson, H., and Larimore, L. D. *Diabetes Mellitus. A Contribution to Its Epidemiology Based Chiefly on Mortality Statistics*, Arch Int Med **34** 585 (Nov) 1924.

15 (a) Joslin, E. P. *Diabetes. Its Control by the Individual and the State*, Boston, Harvard University Press, 1931, p. 46, (b) *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 675, (c) *The Ten-Year Diabetic*, Am J M Sc **175** 472, 1928.

16 Joslin, E. P., Dublin, L. I., and Marks, H. H. *Studies in Diabetes Mellitus. Characteristics and Trends of Diabetes Mortality Throughout the World*, Am J M Sc **186** 753, 1933.

females, as in John's<sup>17</sup> first series of 1,000 cases. In New York City, however, deaths from diabetes, as recorded in death certificates, showed the unusual sex distribution noted in my series<sup>18</sup>. Among 1,784 patients dying of diabetes in 1930 there was an equal proportion of males and of females up to the age of 35. After this age the percentage of females increased, until at 55 and over the ratio of females to males was 2:1. Joslin, Dublin and Marks<sup>16</sup> recently found a similar distribution in the mortality of holders of industrial life insurance policies. In Wendt and Peck's<sup>19</sup> analysis, the ratio of females to males was 3:1 in the sixth decade, and more than 2:1 in the fifth. A high incidence of females among patients with diabetes past the fourth decade probably represents an accurate estimate of the typical sex distribution.

*Relation of Cardiovascular Abnormalities to Age and Sex*—All the cardiovascular variants studied show a higher incidence in females than in males (table 3). The least variation by sex was in the case of atherosclerosis of the aorta, the greatest for transient hypertension. The differences for retinitis and electrocardiographic abnormalities were slight in comparison with those for hypertension and cardiac enlargement. Kramer<sup>6</sup> found a similar sex linking for hypertension among his diabetic patients.

The incidence of each cardiovascular variant is higher in the sixth decade than in the fifth. After the sixth decade atherosclerosis of the aorta, hypertension and abnormalities of the electrocardiogram continue to increase in frequency. The incidence of the other abnormalities diminishes slightly, but the frequency of enlargement of the heart drops sharply. The reasons for this have already been discussed. The increasing incidence of most cardiovascular abnormalities in persons with diabetes with advancing age has been generally recognized,<sup>20</sup> it parallels similar increases among nondiabetic persons. Only in respect to hypertension,<sup>5</sup> and less satisfactorily in respect to calcification of the peripheral arteries,<sup>21</sup> have direct comparisons at comparable ages

17 John, H. J. Diabetes. A Statistical Study of One Thousand Cases, *Arch Int Med* **39** 67 (Jan) 1927.

18 *Week Bull*, New York City Health Dept **20** 357, 1931.

19 Wendt, L. F. C., and Peck, F. B. Diabetes Mellitus. A Review of 1,073 Cases, 1919-1929, *Am J M Sc* **181** 52, 1931.

20 Morrison, L. B., and Bogan, I. K. Calcifications of the Vessels in Diabetes, *J A M A* **92** 1424 (April 27) 1929. Gray, P. A., and Sansum, W. D. The Higher Carbohydrate Diet Method in Diabetes Mellitus, *ibid* **100** 1580 (May 20) 1933. Leutenegger, F. Diabetes Mellitus und Gefasssystem, *Ztschr f klin Med* **119** 164, 1931.

21 Bowen, B. D., and Koenig, E. C. Arteriosclerosis and Diabetes Including a Roentgenological Study of the Lower Extremities, *Bull Buffalo Gen Hosp* **5** 31 1927.

been made to determine the relative frequency in diabetic and non-diabetic persons. These indicate a higher frequency in persons with diabetes.

*Relation of Cardiovascular Abnormalities to the Severity and Duration of Diabetes*—Because of the lack of directly comparable data on the relative incidence of cardiovascular abnormalities in diabetic and

TABLE 5—Percentage Incidence of Cardiovascular Abnormalities by Age and Severity of Diabetes

	Retinal Arterio sclerosis		Retinitis		Aortic Athero sclerosis, Grades 2 and 3		Hyper tension		Enlarged Heart, Grades 1, 2 and 3		Abnormal Electro cardiogram T <sub>12</sub> and Conduction Defects	
	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
40 to 49 years	50%	42%	11%	17%	29%	33%	52%	44%	45%	29%	29%	7%
50 to 59 years	82%	82%	18%	64%	69%	40%	58%	42%	71%	44%	42%	36%
60 years and over	82%	67%	33%	33%	83%	73%	70%	65%	46%	40%	38%	62%
Total	73%	63%	22%	37%	64%	53%	62%	52%	51%	37%	36%	33%
Number of cases	100		100		82		118		100		117	

TABLE 6—Percentage Incidence of Cardiovascular Abnormalities by Age and Duration of Diabetes

	Retinal Arterio sclerosis		Retinitis		Aortic Athero sclerosis, Grades 2 and 3		Hyper tension		Enlarged Heart, Grades 1, 2 and 3		Abnormal Electro cardiogram T <sub>12</sub> and Conduction Defects	
	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over	Less Than 5 Years	5 Years and Over
40 to 49 years	44%	50%	6%	22%	25%	36%	44%	53%	41%	38%	29%	11%
50 to 59 years	88%	77%	23%	46%	50%	78%	53%	50%	64%	55%	35%	43%
60 years and over	85%	70%	38%	30%	80%	76%	68%	68%	59%	33%	50%	43%
Total	71%	67%	22%	31%	54%	64%	55%	59%	54%	39%	39%	33%
Number of cases	99		99		81		117		99		115	

nondiabetic persons, it is necessary to attack the problem of the effect of diabetes on the cardiovascular system by induction. This has been attempted here by the correlation of each variant with the severity and duration of diabetes. The results are shown in tables 5 and 6.

The criteria used in separating the mild from the severe cases are given in the footnotes to table 1. They are in part arbitrary and open to criticism on several grounds. Rabinowitch,<sup>22</sup> for instance, suggested

<sup>22</sup> Rabinowitch, I. M. The Cholesterol Content of Blood Plasma in Diabetes Mellitus, Arch Int Med 43:363 (March) 1929.

the blood cholesterol level as a more reliable index of severity. This would seem important, particularly as it applies to the effect on the arterial system, but Shepardson<sup>23</sup> observed no notable differences in blood cholesterol in young diabetic patients with and without roentgenographic evidence of peripheral arteriosclerosis.

Retinitis is more frequent in severe than in mild cases of diabetes. In the sixth decade it is three and one-half times as frequent. Despite the fact that the retinitis of the diabetic patient is essentially an arteriosclerotic retinitis increasing in frequency with age, it is also directly influenced by the disturbance of carbohydrate metabolism. Only after the sixth decade is the incidence as high in the mild as in the severe cases.

With the one further exception of an abnormal electrocardiogram after the sixth decade, every other cardiovascular variant is more frequent, in the mild as in the severe cases, or at least as frequent. This seems to confirm the suggestion of some investigators<sup>24</sup> that diabetes has little if any effect on the severity of arteriosclerosis. Joslin, however, has offered abundant proof to the contrary, some of it hypothetical, but most of it factual and based on clinical and pathologic grounds, as well as on statistics of contributory causes of death.<sup>25</sup> It is to be noted that table 5 does not indicate that severe diabetes has no effect on the incidence of cardiovascular abnormalities. It seems to indicate that mild diabetes has a more pronounced effect than severe diabetes. This is a clue worth pursuing because it leads to another approach which is more in conformity with Joslin's views.

The diabetic population is not stationary. In each succeeding decade of life in the general population there are new diabetic recruits. At advanced ages the patients with recently acquired diabetes are not arteriosclerosis-free, in fact, they may have severe cases of arteriosclerosis, and it is well known that in these patients the disturbance of carbohydrate metabolism may be only slight. It is therefore not surprising to notice a close association between mild diabetes and the higher percentages of incidence of cardiovascular abnormalities.

If this explanation is correct, a high incidence of cardiovascular abnormalities should be found in cases of diabetes of recent origin in persons of advanced ages. This is demonstrated in table 6. With exceptions at some ages (but chiefly before the sixth decade), the incidence is higher in cases with a duration of less than five years than in those of five years' standing and over. The significance of these

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23 Shepardson, H. C. Arteriosclerosis in the Young Diabetic Patient, *Arch Int Med* **45** 674 (May) 1930.

24 Nathanson<sup>3</sup> Enklewitz, M. Diabetes and Coronary Thrombosis, *Am Heart J* **9** 386, 1934.

25 Joslin,<sup>1, b</sup> pp 375 and 678.

facts is that elderly persons with severe arteriosclerosis in whom diabetes develops have cardiovascular abnormalities more frequently than persons in whom diabetes began earlier. The probable effect of diabetes on the initiation or intensification of arteriosclerosis is concealed in the tables by the accretion of new diabetic patients, already severely arteriosclerotic. These facts do not contradict the views of Joslin's school, neither do they, except indirectly, confirm them.

#### TYPES OF CARDIOVASCULAR DISEASE IN DIABETIC PATIENTS

*Rheumatic and Syphilitic Cardiovascular Disease*—Rheumatic fever does not concern the diabetic patient, if only because of the wide divergence in the ages of onset. The cardiac sequelae of rheumatic fever are found in only a very small percentage of cases of diabetes. Concerning the arterial sequelae, there is as yet almost complete ignorance as concerns the nondiabetic and, perforce, the diabetic patient. In the absence of active infection rheumatic fever may be relegated to a place of minor importance, as to the manner in which it affects both the heart and the blood vessels of diabetic patients. Barach<sup>26</sup> found a history of rheumatic fever as frequent for his diabetic as for his nondiabetic patients, but the cardiac sequelae were much less frequent in the former group. He attributed this to a hereditary constitutional immunity of the potential diabetic patient to the cardiac lesions of rheumatic fever, a view of considerable interest in the light of the theories which link diabetes to the pituitary gland and the autonomic centers in the diencephalon.<sup>27</sup> In this series, there was but 1 instance of rheumatic endocarditis, and this was an inactive, healed lesion. The slightly higher incidence of other forms of arthritis in diabetes has no known bearing on the cardiovascular system.

Syphilis also is relatively uncommon in cases of diabetes. In this series there were 3 patients (2.5 per cent) with positive Wassermann reactions. Joslin<sup>28</sup> noted syphilis in 1.9 per cent of his cases, John,<sup>29</sup> in 2.7 per cent, although he cites higher per cents found by some other investigators. Accordingly, syphilitic aortitis, aneurysm and aortic insufficiency may be disregarded as infrequent in coincidence with diabetes. The possibility of a higher incidence of syphilitic myocarditis

26 Barach, J. H. The Incidence of Rheumatic Heart Disease Among Diabetic Patients, *Am Heart J* 2:196, 1926.

27 Penfield, W. The Influence of the Diencephalon and Hypophysis upon General Autonomic Functions, *Bull New York Acad Med* 9:613, 1933.

28 Joslin,<sup>15b</sup> p. 754.

29 John, H. J. Diabetes. A Statistical Study of Two Thousand Cases, *Arch Int Med* 42:217 (Aug) 1928.

in the absence of positive serologic reactions formerly a widely accepted theory, has fallen into disrepute, so that even Waithin<sup>30</sup> shifted his attention from the myocardium to the coronary arteries. He admitted that the coronary lesions are not always the direct result of syphilitic disease although apparently more frequent in those with syphilitic lesions elsewhere. In the absence of more patients with positive Wassermann reactions, the cardiac and arterial sequelae of syphilis may be considered to be of little importance in diabetes.

*Clinical Types of Arteriosclerosis*—The importance of arteriosclerosis in diabetic patients and its predominant localization in the coronary arteries and the peripheral arteries of the lower extremities have been widely recognized. Joslin<sup>31</sup> has demonstrated the increasing incidence of the cardiovascular, and particularly of the cardiac, mode of death. Numerous other observers have testified to the frequency of coronary arteriosclerosis<sup>32</sup> and coronary thrombosis<sup>33</sup>.

The classification of arteriosclerosis occurring among diabetic patients has been limited pathologically to localization of the predominant sites of sclerosis. Warren<sup>32a</sup> also differentiated the lesions in the large arteries according to whether they were chiefly elastic or muscular, the chief lesion of the former type being atheroma, and that of the latter, medial calcification. He found the atheromatous type the outstanding one, and the intimal involvement of muscular arteries the most characteristic arterial lesion in diabetes. Aside from this, arteriosclerosis has been considered a single disease entity. Allbutt vigorously disputed this view and insisted on the necessity for a clinical differentiation of arteriosclerosis, which is not a disease but the end-result in the arteries of many varied influences. He described two clinical types which are of interest here, namely, decrescent or degenerative arteriosclerosis and hyperpiesis<sup>34</sup>. A less confusing name for the latter is diffuse hyper-

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30 Waithin, A. S. The Role of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis and of Sudden Cardiac Death, *Tr. A. Am. Physicians* **45** 123, 1930.

31 Joslin,<sup>15b</sup> p. 676.

32 Warren,<sup>4</sup> pp. 124 and 148. Wilder, R. M. Necropsy Findings in Diabetics, *South. M. J.* **19** 241, 1926. Von Noorden, C. *Die Zuckerkrankheit und ihre Behandlung*, ed. 5, Berlin, A. Hirschwald, 1910, p. 189. Blotner, H. Coronary Disease in Diabetes Mellitus, *New England J. Med.* **203** 709, 1930. Root, H. F., and Graybiel, A. Angina Pectoris and Diabetes Mellitus, *J. A. M. A.* **96** 925 (March 21) 1931. Nathanson.<sup>3</sup>

33 (a) Joslin,<sup>15b</sup> Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* **8** 245, 1929.

34 Allbutt, T. C. *Arteriosclerosis. A Summary View*, New York, The Macmillan Company, 1925, *Diseases of Arteries Including Angina Pectoris*, New York, The Macmillan Company, 1915.

plastic sclerosis<sup>35</sup> A third common clinical type of arteriosclerosis has also been described It has been variously named malignant arteriosclerosis, malignant hypertension,<sup>36</sup> the malignant phase of essential hypertension<sup>37</sup> and malignant nephrosclerosis<sup>38</sup> Diabetes is rare in association with this clinical type of arterial lesion

One hundred cases in this series have been classified in accordance with the descriptions of these types of arteriosclerosis Under degenerative arteriosclerosis are included all cases in which the heart was normal or only slightly enlarged, under diffuse hyperplastic sclerosis, those in which the heart was enlarged Among the latter are included 3 cases without hypertension in which the large heart was considered evidence of preexisting hypertension The cases of degenerative arteriosclerosis have been further differentiated by the presence or

TABLE 7—*Sex Distribution by Clinical Type of Arteriosclerosis in One Hundred Cases*

Type of Arteriosclerosis	Male	Female	Total
Degenerative arteriosclerosis without hypertension	17	20	37
Degenerative arteriosclerosis with hypertension	2	43	45
Diffuse hyperplastic sclerosis	3	15	18

TABLE 8—*Age Distribution by Clinical Type of Arteriosclerosis in One Hundred Cases*

Type of Arteriosclerosis	40 to 49 Years	50 to 59 Years	60 Years and Over
Degenerative arteriosclerosis without hypertension	16	9	12
Degenerative arteriosclerosis with hypertension	14	9	22
Diffuse hyperplastic sclerosis	3	7	8

absence of hypertension The age and sex distribution of the clinical types of arteriosclerosis is shown in tables 7 and 8

The most frequent clinical type of arteriosclerosis associated with diabetes is degenerative arteriosclerosis (82 per cent) Diffuse hyperplastic sclerosis is much less frequent (18 per cent), and there were no patients in this series with malignant arteriosclerosis Slightly more than one half of the patients with degenerative arteriosclerosis, mostly women, had hypertension (55 per cent) The age distribution indi-

35 Evans, G A Contribution to the Study of Arteriosclerosis, *Quart J Med* **14** 215, 1921

36 Keith, N M, Wagener, H P, and Kernohan, J W The Syndrome of Malignant Hypertension, *Arch Int Med* **41** 141 (Feb) 1928

37 Fishberg, A M Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930

38 Klempeier, P, and Otani, S Malignant Nephrosclerosis (Fahr), *Arch Path* **11** 60 (Jan) 1931



cates a rather high incidence of diffuse hyperplastic sclerosis in the persons in the sixth decade. In persons in the fifth decade many cases of mild arteriosclerosis are included under degenerative arteriosclerosis.

The clinical type of arteriosclerosis bears a direct relationship to the percentage of cases of severe diabetes with which each type is associated (table 9). One half of the cases of degenerative arteriosclerosis without hypertension, and almost two thirds of those of degenerative arteriosclerosis with hypertension were in persons with mild diabetes. Four fifths of the cases of diffuse hyperplastic sclerosis were in persons with mild diabetes.

Table 10 shows the relation of retinal arteriosclerosis, aortic arteriosclerosis, retinitis and abnormal electrocardiograms to the clinical type

TABLE 9—*Percentage Incidence of Severe Diabetes by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	Incidence of Severe Diabetes
Degenerative arteriosclerosis without hypertension	49%
Degenerative arteriosclerosis with hypertension	38%
Diffuse hyperplastic sclerosis	18%

TABLE 10—*Percentage Incidence of Cardiovascular Abnormalities by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	Retinal Arterio sclerosis	Aortic Athero sclerosis, Grades 1, 2 and 3	Aortic Athero sclerosis, Grades 2 and 3	Retinitis	Abnormal Electro cardiogram T <sub>12</sub> and Conduction Defects
Degenerative arteriosclerosis without hypertension	36%	61%	39%	14%	26%
Degenerative arteriosclerosis with hypertension	72%	77%	66%	23%	29%
Diffuse hyperplastic sclerosis	93%	94%	88%	43%	63%

of arteriosclerosis. The lowest incidence of each of these variants occurred in persons with degenerative arteriosclerosis without hypertension. In persons with degenerative arteriosclerosis with hypertension, the percentages were consistently higher, and in those with diffuse hyperplastic sclerosis they were highest. The same relationship to the clinical type of arteriosclerosis is demonstrated in the incidence of cardiac symptoms, cardiac decompensation, cardiac pain of all types and angina pectoris (table 11). These two tables indicate that the frequency of clinically recognizable arteriosclerosis in the retina and aorta, retinitis, abnormalities of the electrocardiogram and cardiac symptoms, including pain and cardiac decompensation, bears a direct relation to the clinical type of arteriosclerosis as determined by the size of the heart and the blood pressure.

## EVALUATION OF CARDIOVASCULAR ABNORMALITIES

Gangrene of the lower extremities may be taken as *prima facie* evidence of severe arteriosclerosis, not only in the arteries of the leg but in the coronary and other important vascular branches. Cerebral or coronary thrombosis has the same significance. The presence of the last mentioned condition indicates the most probable mode of death, but the presence of widespread vascular lesions may lead a patient with gangrene of the foot, successfully treated, to a fatal end through closure of the cerebral or coronary arteries. Any combination of these terminal events is possible in the diabetic patient who avoids the pitfalls of coma and infection until an advanced age. The management of the arteriosclerotic patient who also has diabetes requires an evaluation of the extent, severity and type of the arterial pathologic condition.

The severity of aortic atherosclerosis and the presence of dilatation or calcification afford a fairly reliable index of the severity of the general vascular disease. The same is true of the extent of calcification

TABLE 11—*Percentage Incidence of Cardiac Symptoms, Cardiac Decompensation, Cardiac Pain and Angina Pectoris by Clinical Type of Arteriosclerosis*

Type of Arteriosclerosis	All Cardiac Symptoms	Cardiac Decompensation	Cardiac Pain	Angina Pectoris
Degenerative arteriosclerosis without hypertension	24%	0%	5%	0%
Degenerative arteriosclerosis with hypertension	51%	13%	18%	11%
Diffuse hyperplastic sclerosis	67%	17%	39%	22%

of the arteries of the lower extremities. It is somewhat more difficult to grade the severity of retinal arteriosclerosis, and it is questionable whether, aside from determining the presence or absence of the condition, this would be useful in determining the state of the general arterial tree. All these evidences of general vascular diseases are frequent in elderly diabetic patients, and it sometimes is difficult to deduce from them in more than general terms any prognostic conclusions. A more valuable guide is the clinical type of arteriosclerosis. The general arterial disease is more widespread and, consequently, of greater importance in diffuse hyperplastic sclerosis than in degenerative arteriosclerosis, and in the latter type of cases, those with hypertension are more likely to be accompanied by cardiac sequelae.

Nathanson<sup>3</sup> has shown that the incidence of coronary sclerosis is directly proportional to the size of the heart. The clinical determination of the type of arteriosclerosis, based as it is chiefly on cardiac enlargement, consequently indicates the relative importance of arteriosclerosis in the coronary arteries and, by that token, also of general arteriosclerosis.

*Significance of Retinitis*—The prognostic significance of arteriosclerotic retinitis depends on the clinical type of arteriosclerosis in which

it is found and, more importantly, on the presence or absence of diabetes. In the nondiabetic patient, Moore<sup>8</sup> demonstrated its association with the cerebral mode of death. This association applies particularly to diffuse hyperplastic sclerosis and, to some extent, to degenerative arteriosclerosis. In malignant arteriosclerosis, in which retinitis and also papilledema are almost invariably present, the terminal events are more likely to be uremic or cardiac. Keith Wagener and Kernohan<sup>36</sup> reported that frequently combinations of uremic, cerebral and cardiac events closed the clinical picture. In cases of diabetes with arteriosclerosis the most frequent modes of death (excluding coma and infection) are cardiac failure and coronary thrombosis. Retinitis may be considered, by virtue of its origin, as an indicator of this type of cardiovascular end in the diabetic patient. Actually, it indicates that the general pathologic condition of the entire arterial tree is severe.

The linking of retinitis to the general vascular disease in cases of diabetes does not, however, exclude a subsidiary link to the disturbance of carbohydrate metabolism. Retinitis not only increases in frequency with age and the coincident increase in vascular disease, it is more frequent in severe than in mild cases of diabetes and in cases of long duration. It is also a reversible phenomenon. In 4 cases in this series, hemorrhages and even so-called areas of retinal degeneration disappeared under observation. These factors may be summarized as follows: age and an advancing pathologic condition of the arteries predispose to retinitis, the disturbance of carbohydrate metabolism, particularly if poorly controlled, initiates it.

#### *Significance of the Abnormal T Wave in the Electrocardiogram —*

The important electrocardiographic abnormalities observed in patients with diabetes are defects in conduction (widening of the QRS complex and prolonged auriculoventricular conduction time) and anomalies of the T wave. Of these, the aberrations of the T wave are more frequent. The minor notches and slurs of the QRS complex which have been reported<sup>39</sup> may be disregarded, and the prognostic value of low voltage QRS and deep Q<sub>3</sub> are still questionable. What is known of the physiologic processes involved in the production of abnormalities of the T wave throws little light on their relation to diabetes. Lewis<sup>40</sup> dismissed the subject with a footnote. Katz<sup>41</sup> has shown that the anomalies are

39 Blitzsten E P W, and Schram, D L. Diabetes. Electrocardiographic Studies, Arch Int Med 36 770 (Dec) 1925

40 Lewis, T. Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1925, p 122

41 Katz, L N. The Significance of the T Wave in the Electrogram and the Electrocardiogram. Physiol Rev 8 447, 1928

not pathognomonic of any clinical entity. Ordinarily, they are said to signify myocardial disease or coronary disease, but these are vague terms and far from helpful. The so-called coronary T wave is not found exclusively in coronary disease, conversely, coronary atherosclerosis may be present without the cove-shaped T wave or without the  $T_1$  or  $T_2$  type of disturbance of the ST segment, and in fact without any abnormality of the T wave. The expressions "myocardial disease" and "coronary disease" as applied to changes of the T wave cover a wide range of possible anatomic and physiologic variations, some not at all related to the heart. Furthermore, many of these abnormalities are reversible, even without coronary thrombosis. For these reasons, the interpretation of an abnormal T wave depends on the clinical milieu in which it is found. In cases of diabetes, the abnormal T wave and conduction defects are found under the following circumstances:

- 1 In diabetic coma, dehydration affects the skin capacity so that electrocardiograms are so distorted as to make it frequently impossible to ascertain whether or not the T wave is normal. In addition to these changes, Faulkner and Hamilton<sup>42</sup> reported 2 cases of abnormal T wave in 15 cases of coma. One of the patients recovered and later had a normal control record. They also noted that in 3 cases in which the electrocardiogram was normal during coma it was abnormal later.

- 2 In hypoglycemic states, minor changes are found, with subsequent restitution to normal.<sup>43</sup>

- 3 Infection may produce changes in the electrocardiogram. Case 112 illustrates this. In 1931, the electrocardiogram was normal. In 1932, pulmonary tuberculosis was reactivated, with coincident diminution of carbohydrate tolerance and the appearance of an abnormal T wave in lead II. The flat  $T_1$  wave in case 9 may also be due to infection. Similar temporary aberrations occur in many acute infections in nondiabetic cases.

- 4 Temporary abnormalities appear in phases of the loss of carbohydrate tolerance when uncontrolled and without any other complicating factor. Smith and Hickling<sup>44</sup> described increases in amplitude of the upright T wave after dietetic standardization, chiefly in young patients. They also reported 2 cases of  $T_{12}$  inversions which came upright, one

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42 Faulkner, S. M., and Hamilton, B. E. The Electrocardiogram in Diabetic Coma, *Am Heart J* **8** 691, 1933.

43 Middleton, W. S., and Oatway, W. H. Insulin Shock and the Myocardium, *Am J M Sc* **181** 39, 1931. Soskin, S., Katz, L. N., Strouse, S., and Rubinfeld, S. H. Treatment of Elderly Diabetics with Cardiovascular Disease. *Arch Int Med* **51** 122 (Jan) 1933.

44 Smith, K. S., and Hickling, R. A. Electrocardiographic Changes During Treatment of Severe Diabetes, *Lancet* **1** 501, 1932.

in a few weeks and the other after fifteen weeks. Cases 21 and 28 illustrate similar changes. Neither patient had infection or cardiac symptoms. In the first, the elevation of the T wave was progressive, requiring one year, in the second admitted in a precomatose state, the change occurred after one week in the hospital.

5 The most frequent cause of electrocardiographic abnormalities is arteriosclerosis and its sequelae. The cases due to dehydration, infection, hypoglycemia or loss of carbohydrate tolerance are few in comparison with the many in which the cause is directly related to the arterial pathologic condition. This has already been indicated in the data presented, which may be summarized as follows. The incidence of electrocardiographic abnormalities increases with age, like retinitis, they are only slightly more frequent in females than in males, no direct relationship could be demonstrated to either the severity or the duration of diabetes, and the incidence is directly related to the clinical type

TABLE 12—*Percentage Incidence of Abnormal Electrocardiogram by Clinical Type of Arteriosclerosis and Cardiac Sequelae*

Type of Arteriosclerosis	Without Cardiac Symptoms	With Cardiac Symptoms	With Cardiac Decomensation	With Cardiac Pain	With Angina Pectoris
Degenerative arteriosclerosis without hypertension	22%	38%	No cases	0%	No cases
Degenerative arteriosclerosis with hypertension	18%	39%	57%	50%	50%
Diffuse hyperplastic sclerosis	20%	75%	100%	86%	75%

of arteriosclerosis. Two other facts are pertinent. In 7 cases (cases 10, 31, 83, 87, 104, 116 and 120), an abnormal electrocardiogram appeared while the patient was under observation, when under good conditions of metabolic control and without any complicating infection. In 4 other cases (cases 24, 76, 94 and 112) there was a complicating infection. In the 7 cases in which arteriosclerosis alone was involved, none of the patients had coronary thrombosis. The appearance of the abnormal electrocardiogram was associated with cerebral thrombosis in case 10 and with progressive loss of vision due to retinitis in case 31. Finally, it should be noted that abnormal electrocardiograms are found in about one fifth of the cases in which there are no cardiac symptoms (table 12). With cardiac symptoms and decompensation, the percentages increase, and with retinitis, abnormal electrocardiograms are two and one-half times as frequent as without retinitis.

6 Abnormalities of the T wave may also be due to factors as yet unknown, possibly in association with disturbances of the autonomic nervous system.

To summarize, abnormal T waves in cases of diabetes are seen under the following conditions infection, disturbances of carbohydrate and water metabolism and general arteriosclerosis (including coronary sclerosis and thrombosis) The changes due to the first two conditions may be transient They are probably the result of reversible processes in the cardiac muscle or neuromuscular tissues Changes due to advanced arteriosclerosis are irreversible, both pathologically and in the electrocardiogram Excluding the transient abnormalities of the T waves due to causes other than coronary thrombosis, electrocardiographic abnormalities should be considered evidences of advanced general arteriosclerosis In this respect, the significance of the abnormal electrocardiogram is similar to that of retinitis

#### SUMMARY AND CONCLUSIONS

1 In a series of 120 cases of diabetes mellitus in persons above the age of 39, arteriosclerosis was demonstrable by clinical methods in the aorta in 75 per cent of the patients, of whom 60 per cent had aortic dilatation, in the retinal arteries in 69 per cent, in either the aorta or the retina in 89 per cent, and in both in 51 per cent

2 The heart was enlarged in 47 per cent of the cases, but in only 18 per cent was the enlargement more than slight Cardiac enlargement is less frequent in patients with diabetes past the fourth decade of life than in nondiabetic patients with arteriosclerosis

3 Hypertension was present in 56 per cent of the cases but was transient in all but 38 per cent, retinitis occurred in 28 per cent of the cases, and electrocardiographic abnormalities (T wave abnormalities and conduction defects), in 35 per cent

4 After the fourth decade of life, female diabetic patients outnumber the male patients two or three times

5 Nine tenths of all diabetic patients live at ages at which they are exposed to the risk of arteriosclerosis from causes other than diabetes

6 Cardiovascular abnormalities in diabetic patients after the fourth decade are more frequent in females than in males

7 The incidence of retinitis, retinal arteriosclerosis, aortic arteriosclerosis, hypertension and abnormalities of the electrocardiogram increases with age

8 The incidence of cardiac enlargement diminishes abruptly after the sixth decade

9 Retinitis is more frequent in cases of severe than in those of mild diabetes

10 Retinitis is more frequent in cases of diabetes of long than in those of short duration

11 Diabetic patients with severe arteriosclerosis and a high incidence of cardiovascular abnormalities, other than retinitis tend to have mild diabetes

12 Arteriosclerotic patients of advanced ages whose diabetes is of recent origin tend to have a higher incidence of cardiovascular abnormalities than those of the same age group in whom diabetes began earlier

13 Rheumatic fever and syphilis are minor factors in the development of cardiovascular disease in diabetic patients

14 Diabetic patients with arteriosclerosis have two distinctive types of arteriosclerosis. Most of them have degenerative arteriosclerosis, and a small percentage have diffuse hyperplastic sclerosis

15 Among patients with degenerative arteriosclerosis without hypertension there are as many with mild as with severe diabetes, in those with degenerative arteriosclerosis with hypertension, the mild cases predominate, of those with diffuse hyperplastic sclerosis, four fifths have mild diabetes

16 The incidence of all cardiovascular abnormalities studied is highest in patients with diffuse hyperplastic sclerosis, lower in those with degenerative arteriosclerosis with hypertension and lowest in those with degenerative arteriosclerosis without hypertension. The clinical type of arteriosclerosis also determines the incidence of cardiac symptoms and sequelae

17 Retinitis and the abnormalities of the electrocardiogram are chiefly indexes of an advanced arterial pathologic condition in the choroidal and coronary arteries, but other factors are also involved in determining their initiation. Clinically, the presence of these abnormalities usually signifies advanced general arteriosclerosis

# SECRETION OF MUCUS AND ACID BY THE STOMACH IN HEALTHY PERSONS AND IN PERSONS WITH PEPTIC ULCER

H NECHELES, M D, P H D

AND

A COYNE, M D

ASSISTED BY H GROSS

CHICAGO

The importance of gastric mucus as a neutralizer of gastric acidity and as a protective coating mechanism has been stressed by Heidenhain,<sup>1</sup> Pavlov<sup>2</sup> and his school, Zweig,<sup>3</sup> Webster,<sup>4</sup> Bolton and Goodhart,<sup>5</sup> Fogelson,<sup>6</sup> Kim and Ivy,<sup>7</sup> Babkin and Komarov<sup>8</sup> and a number of other workers<sup>9</sup>. Differing views have recently been advanced by Bonis,<sup>10</sup> Kalk and Bonis<sup>11</sup> and Mitchell<sup>12</sup>.

The work reported here was undertaken in order to find how much visible mucus and acid is secreted by persons suffering from peptic ulcer as compared with that secreted by normal persons. It was thought that a difference in the amount of mucus secreted by the two groups might be indicative of the protective mechanism of mucus against autodiges-

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1 Heidenhain, R., in Hermann, L. *Handbuch der Physiologie*, Leipzig, F. C. W. Vogel, 1883, vol. 5, p. 122.

2 Pavlov, I. P. *The Work of the Digestive Glands*, London, C. Griffin & Company, 1910.

3 Zweig, W. *Arch f. Verdauungskr.* **12** 364, 1906.

4 Webster, D. R. *Am. J. Physiol.* **90** 718, 1929.

5 Bolton, C., and Goodhart, G. W. *J. Physiol.* **73** 115, 1931, **77** 287, 1933.

6 Fogelson, S. J. *Treatment of Peptic Ulcer with Gastric Mucin*, *J. A. M. A.* **96** 673 (Feb. 28) 1931.

7 Kim, M. L., and Ivy, A. C. *Prevention of Experimental Duodenal Ulcer by Feeding Neutral Gastric Acid*, *J. A. M. A.* **97** 1511 (Nov. 21) 1931.

8 Babkin, B. P., and Komarov, S. A. *Canad. J. M. A.* **27** 463, 1932.

9 Babkin, B. P. *Die aussere Sekretion der Verdauungsdrusen*, Berlin, Julius Springer, 1928, p. 364.

10 Bonis, A. *Ztschr. f. klin. Med.* **113** 611, 1930.

11 Kalk, H., and Bonis, A. *Deutsches Arch. f. klin. Med.* **173**.53, 1932.

12 Mitchell, T. C. *J. Physiol.* **73** 427, 1931.



tion of the stomach or the first part of the duodenum. The improbability of a protection of the duodenum by antitrypsin has been demonstrated in earlier papers<sup>13</sup>

Gastric mucus is secreted by the cylindric surface epithelium<sup>1</sup> and by the mucoid cells in the tubular glands<sup>14</sup>. Most gastric juices contain two varieties of mucus, one of which has a visible form, which frequently assumes a threadlike appearance in a fresh specimen of gastric contents and often forms lumps. This mucus usually contains a higher amount of pepsin than the supernatant gastric juice<sup>15</sup>. The high pepsin content and the threadlike structure suggest that it is secreted by the mucoid cells in the tubular glands. The second form of mucus found in gastric juice is in solution and may be precipitated by various means<sup>16</sup>. According to Webster and Komarov,<sup>16</sup> the two types of mucus are chemically different, the visible mucus is secreted by the surface epithelium, while the dissolved mucus originates from the glandular part of the stomach.

It is known from the work of Pavlov<sup>2</sup> and others that a variety of substances increase the mucus secreted by the stomach.<sup>9</sup> Bread and a number of other substances that act physically or chemically, like hot water, alcohol, silver nitrate and volatile oil of mustard, or secretagogues, like pilocarpine, belong to this group.

#### METHODS AND MATERIAL

*Method*—Pilocarpine was chosen to stimulate the secretion of mucus in order to avoid the introduction of material into the stomach. Four milligrams of pilocarpine nitrate was injected subcutaneously. Salivation, lacrimation and flushes occurred in most instances, but no untoward effects were observed. A Rehfuß tube, swallowed by the patient, was connected through a bottle to suction which was kept constant between 6 and 8 cm. of mercury by a manometer and a needle valve. Another Rehfuß tube was put into the mouth of the subject and connected to a second bottle with suction, to remove saliva (the subjects were instructed not to swallow any). Every ten minutes the bottle with the gastric contents was removed and put into an icebox immediately. There were four ten minute periods before the injection of pilocarpine and six (a number of times, eight) after it. Each specimen of a ten minute aspiration was put into a graduate centrifuge tube and centrifugated at 1,600 rotations per minute for ten minutes. The amount of visible mucus was read and 1 cc. samples of the supernatant gastric juice taken for the titration of free and combined acid. In a number of tests the acidity of the visible mucus was titrated also, and chlorine was determined in mucus and supernatant juice.

13 Necheles, H., Ling, J., and Fernando, F. *Am J Physiol* **79** 1, 1926.  
Necheles, H., and Fernando, F. *ibid* **79** 9, 1926. Necheles, H. *Chinese J Physiol* **2** 229, 1928.

14 Lim, R. K. S. *Quart J Micr Sc* **66** 187, 1922.

15 Brestkin, M. P., and Bickoff, K. M. *J russe de physiol* **7** 301, 1924; quoted by Babkin, p. 365.<sup>9</sup>

16 Webster, D. R., and Komarov, S. A. *J Biol Chem* **96** 133, 1932.

The large amount of data obtained in these studies was treated statistically by the method of R A Fisher,<sup>17</sup> to determine whether the differences denoted real experimental differences rather than accidental biologic variation. In this statement a P value of 0.05 or less is considered to indicate that the variation observed is experimentally significant.

*Subjects*—Our normal subjects were university students and unemployed from the unemployment relief agency. While we considered the former as reliable as our own patients with regard to their history of the use of alcohol, we suspected that part of the latter group indulged in excessive drinking, and in the results we have been careful to look for evidence of alcoholism. The patients were from Mandel Clinic of Michael Reese Hospital and had an established history as well as clinical, laboratory and roentgen evidence of duodenal ulcer. While some histories

TABLE 1—*Subjects of Test for Visible Mucus and Gastric Acidity*

	Number of Subjects	Age Group, Years	Average Age, Years
Normal persons			
Nondrinkers under 40 years of age	19	18 to 40	25
Nondrinkers over 40 years of age	8	42 to 53	49
Drinkers, all ages	10	31 to 51	40
	<hr/> 37		
Patients			
Nondrinkers under 40 years of age	9	20 to 39	32
Nondrinkers over 40 years of age	6	42 to 52	47
Drinkers, all ages	9	33 to 51	45
	<hr/> 24		

TABLE 2—*Duration of Symptoms*

	Duration of Symptoms			
	3 Months to 1 Year	1 to 5 Years	6 to 10 Years	11 to 15 Years
Number of patients	4	10	6	4

were only of from three to eight months' duration, the greater number of patients had a chronic condition. All tests were done in the morning on an empty stomach, no food having been taken for fourteen hours and no heavy meal for twenty hours.

We divided our subjects into two groups, those below and those above 40 years of age, because, according to the statistics of Vanzant, Alvarez, Eusterman, Dunn and Berkson,<sup>18</sup> this age is approximately the dividing line above which gastric acidity in males begins to decline. The normal subjects were white men, except for two Negroes. The patients were all white men, except for two white women, observations on whom were included with those on the men, as there were no evident significant differences.

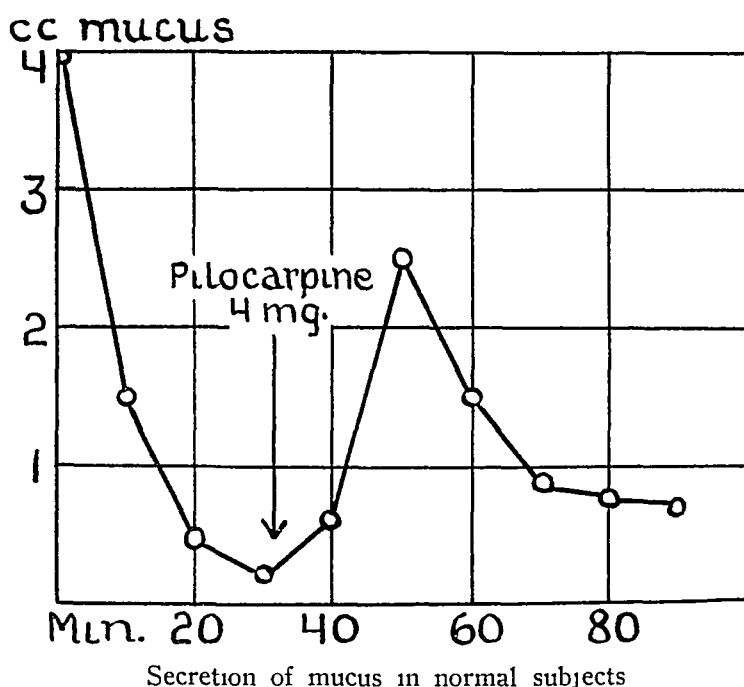
17 Fisher, R A. Statistical Methods for Research Workers, New York, Oxford University Press, 1926, p. 105.

18 Vanzant, F R, Alvarez, W C, Eusterman, G B, Dunn, A L, and Berkson, J. The Normal Range of Gastric Acidity from Youth to Old Age, Arch Int Med 49:345 (March) 1932.

## RESULTS

*Secretion of Mucus*—The nature of the visible mucus makes it necessary to combine several samples taken consecutively. The mucus usually comes in threads and clumps, and sometimes one gets no mucus at all in one sample and a great deal in the next. This is probably due to the method of aspiration. Since the mucus clumps and is not evenly distributed throughout the gastric contents, more may be aspirated during one ten minute period than during the other. The average mucus content of more than one period is therefore more apt to represent the correct figure.

The resting stomach contains mucus, and since the night secretion of acid and mucus by the stomach may be of more importance in case



of ulcer than the day secretion (which is mostly neutralized by food), the volume of mucus of the first two control tests was taken into consideration. In practically all tests, the amount of mucus of the first two control periods was higher than that of the following two control periods, which usually were of the same order of magnitude. Ten minutes after the injection of pilocarpine the volume of mucus usually is not much different from that of the preceding two periods (controls 3 and 4), but from twenty to fifty minutes after the injection of pilocarpine there is an increase of the mucus in the aspirated gastric juice. Sixty and seventy minutes after the injection of pilocarpine the volume of mucus usually returns to the level of the two last controls. The chart illustrates what we found to be typical for many of our tests on normal subjects.

In the Resting Stomach in the Morning The combined volumes of mucus of the first two control periods show a significant increase with age in normal persons who are not habitual consumers of alcohol ( $P < 0.05$ ). The means are 6.31 cc. of mucus in persons below 40 years of age and 10.04 cc. in persons above 40 years of age. Patients with ulcer who do not drink alcohol do not show this increase of mucus with age ( $P > 0.4$ ). The means are 5.92 cc. of mucus in patients below 40 years of age and 7.25 cc. in patients above 40 years of age. While the means of the normal persons appear to be higher than those of the patients with ulcer, statistically there is no significant difference between the volume of mucus of the group of normal persons and the group of patients with ulcer.

Normal persons who are habitual consumers of alcohol and nondrinkers have the same amount of mucus. Drinkers with ulcer have a greater amount of mucus than nondrinkers with ulcer (the means are 12.3 versus 7.25 cc.). This is indicative of associated gastritis in the case of the patients with ulcer who drink alcohol.

Before and After Injection of Pilocarpine While the two age groups of normal subjects and patients had doubtful changes after the injection of pilocarpine, the combined groups of normal subjects and of patients showed a difference. Twenty-seven normal persons who did not consume alcohol had an increase of 0.7 cc. of secretion of mucus after the injection of pilocarpine ( $P = 0.05$ ), and fifteen patients with ulcer who did not drink had only 0.1 cc. ( $P > 0.6$ ). The means of the differences are (in cubic centimeters)

	Before	After	Difference
Normal persons	1.98	2.7	+0.72
Patients with ulcer	1.33	1.46	+0.13

This shows that normal persons have an increase of secretion of mucus after the injection of pilocarpine and that patients with ulcer have none. The group of normal drinkers (all ages combined) showed a borderline decrease of secretion of mucus after the injection of pilocarpine ( $P = 0.54$ ). The mean of the difference is minus 1.5 cc. of mucus (a decrease of 1.5 cc. after the injection of pilocarpine). Since the normal nondrinkers had an increase in the secretion of mucus after the injection of pilocarpine and since the normal drinkers had a decrease, the difference between the two groups is significant ( $P < 0.01$ ).

The free and combined acid of the mucus was usually the same as that of the supernatant gastric juice without visible mucus. Also, the values of the total chlorine of the mucus were within the limits of variation of the supernatant juice.

The clear supernatant juice of all specimens from fifteen patients was used to estimate the amount of dissolved mucus by acetone precipi-

tation<sup>16</sup> No consistent results were obtained Our observations are at variance with those of Anderson, Fogelson and Farmer<sup>19</sup> Their series of four observations on two patients with ulcer and two persons with normal stomachs seems to be too small, however, to decide this question<sup>20</sup>

*Acidity of the Gastric Secretion*—Free Acidity of the Resting Stomach The means of the first control samples of the groups were compared There were no significant differences between the groups of normal persons above and below 40 years of age, whether drinkers or nondrinkers of alcohol But in the patients with ulcer, the group above 40 years of age had a mean acid content much higher than the group of patients under 40 years of age ( $P < 0.01$ ) The mean for the group under 40 years of age was 13 clinical degrees of free acid and that of the group above 40 years of age, 44 degrees These results are not necessarily opposed to those of Vanzant, Alvarez, Berkson and Eusterman,<sup>21</sup> who found a decrease of acidity with age in patients with ulcer as well as in normal persons Their data are based on the response of the stomach to an Ewald test meal, while ours are taken from the first sample of gastric juice withdrawn from the resting stomach in the morning Our values may be representative of the state of secretion during rest, perhaps for the night period From the research of Einhorn and, recently, of Winkelstein<sup>22</sup> and Palmer,<sup>23</sup> it is evident that the stomach of a patient with ulcer secretes more acid at night than does the normal stomach Furthermore, we observed in a number of tests on patients with ulcer that, while there is free acid in the resting stomach, there is no free acid response after the Ewald test meal (one and one and a half hours afterward)

*Combined Acidity of the Resting Stomach* There were either no differences between the groups or only doubtful ones

*Free Acidity Before and After Injection of Pilocarpine* The same averages were compared as in the mucus tests, i. e., the mean of tests 3 and 4 before and of tests 2 to 5 after the injection of pilocarpine After the injection of pilocarpine the free acidity of the group of normal per-

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19 Anderson, R. K., Fogelson, S. J., and Farmer, C. J. *Proc. Soc. Exper. Biol. & Med.* **31** 520, 1934

20 Dr. Fogelson informed us recently that he verified his results in a great number of additional tests

21 Vanzant, F. R., Alvarez, W. C., Berkson, J., and Eusterman, G. B. *Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases*, *Arch. Int. Med.* **52** 616 (Oct.) 1933

22 Winkelstein, A. *Am. J. M. Sc.* **185** 695 (May) 1933

23 Palmer, W. L. *Fundamental Difficulties in the Treatment of Peptic Ulcer*, *J. A. M. A.* **101** 1604 (Nov. 18) 1933

sons over 40 years of age dropped 21.1 clinical degrees (mean of the difference,  $0.02 > P > 0.01$ ). In no other group did such a drop occur.

**Combined Acidity Before and After Pilocarpine** No significant difference for any group was found. We might expect that the mean of the difference before and after the injection of pilocarpine for normal persons above 40 years of age should increase, because the amount of free acid dropped after the injection of pilocarpine. It seems as if pilocarpine causes changes in the secretion of acid and of mucus through a different mechanism.

#### COMMENT

We have not presented the figures for visible mucus in per cent of the total gastric juice, since that would introduce too large an error into the calculations. When the total sample of gastric juice obtained in one period is very small, the mucus (which is mostly coherent) may be recovered completely, while some of the watery fluid may escape. Statistical treatment of all results showed that there were either doubtful or insignificant changes in the percentages of the mucus in the various groups.

The mucus content of the resting stomach is certainly of interest, because it possibly represents the activity of a supposedly protective mechanism during the rest period of the stomach. This assumption is strengthened by our observations that in normal persons the amount of mucus in the resting stomach increases with age, while in patients with ulcer there is no such increase. Patients with ulcer who indulge in alcohol have a greater amount of mucus in their resting stomach than nondrinkers with ulcer. The history of drinking alcohol goes back, in most cases, before the first appearance of symptoms of ulcer. Many of the patients stopped drinking when they realized that they had disease of the stomach. A few continued to drink alcohol because it relieved the pain in the stomach. It is probable that in all or in most of the patients, gastritis was associated with the ulcer.

Normal persons show an increased secretion of mucus after the injection of pilocarpine, while patients with ulcer, drinkers and nondrinkers, do not show such an increase. The group of normal persons who drink alcohol showed a decrease of mucus secretion after the injection of pilocarpine. This lack of reactivity may explain why we found a number of habitual drinkers among patients with ulcer.

It is possible that the reaction of the gastric secretory mechanism to pilocarpine is indicative of the reaction of the stomach to a normal stimulus, like bread, for instance, that is, food provokes an increase of mucus as well as pilocarpine does. The mucus protects the stomach and duodenum physically and perhaps also chemically. Our results indicate that

in the stomach of a normal person such a mechanism is effective, but not in the stomach of drinkers or of persons with duodenal ulcer

We do not want to attach significance to our observations on free and combined acid because, as pointed out earlier, pilocarpine may act on two different places simultaneously, on the acid secretion and on the mucus secretion

All of our patients suffered from duodenal ulcer. Mucus from the stomach may protect this type of ulcer as well as, or even better than, an ulcer in the stomach. The reaction in the upper part of the duodenum tends to be alkaline, the solubility of the visible mucus increases, and it may infiltrate the mucosa <sup>24</sup>

The choice of the age groups in this study was arbitrary, and larger groups may bring evidence of a deficiency in the mechanism of secretion of mucus before the age of 40 (duodenal ulcer occurs chiefly in younger persons). We do not want to conclude from the results that the differences in secretion of the mucus between normal persons and patients with ulcer explain the cause of ulcer. We are rather inclined to assume that the difference in secretion of mucus of the two groups may as well be due to the pathologic condition of the stomach and duodenum as to the causation of the disease

#### SUMMARY

The gastric secretion of visible mucus has been measured after fasting and following the injection of pilocarpine in thirty-seven normal persons and in twenty-four patients with duodenal ulcer. The amount of visible mucus in the stomach after fasting is greater in normal persons above 40 years of age than in normal persons below 40 years of age. This increase with age does not take place in patients with ulcer.

After the injection of pilocarpine, normal persons show an increased secretion of visible mucus, while patients with ulcer (nondrinkers and drinkers of alcohol) do not show such an increase. Normal persons who drink alcohol show a decreased secretion of mucus after the injection of pilocarpine.

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<sup>24</sup> Langenskiöld, F. *Skandinav Arch f Physiol* **31** 1, 1913

# DIET IN CHRONIC ARTHRITIS

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AND  
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Many factors play a rôle in producing one or another form of chronic arthritis. The influence of diet has been given attention, but there have been few studies concerning its etiologic rôle. It has not been unusual to observe considerable improvement in chronic arthritis following the correction of faulty dietary habits, although frequently other therapeutic measures have been employed at the same time. The question arises of the importance of dietary factors in the causation of arthritis. An attempt is made here to reexamine the evidence for the relationship between diet and chronic arthritis, especially the possible etiologic relationship of long-continued, mildly deficient diets.

An evaluation has been made of the dietary history of seventy-five patients with chronic arthritis. There were twenty-seven patients with hypertrophic (degenerative) arthritis, forty with atrophic (rheumatoid) arthritis, and eight with what has been termed chronic infectious arthritis. Six of the latter eight cases were proved to be due to gonococcic infection, and the remaining two were tuberculous in origin. Patients with rheumatic fever and gout were rigidly excluded.

A control group of patients whose dietary habits were studied was made up of thirty persons unselected except that they came from similar social strata and were of the same age and sex distribution as the patients with arthritis. A higher percentage of patients was chosen from the clinic group advisedly. The control group included patients convalescent from lobar pneumonia, with infections of the upper respiratory tract, pulmonary tuberculosis, carbon monoxide poisoning, arterial hypertension and other disorders.

The evaluation of the various constituents of the diet was, of necessity, difficult. The caloric content of the diet of a given patient was said to be excessive when the body weight was increasing or remained considerably above that of the ideal. The diet was termed excessive in carbohydrate foodstuffs when the patient consumed approximately 600 Gm of starch and sugar daily and lived a sedentary life, or when he derived as much as 80 per cent of the caloric content of the diet from the

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food substances just mentioned. The protein content of the diet was considered inadequate when, per week, there were not more than four servings of meat, two or three eggs, little or none of the dairy products and only occasionally a serving of vegetables, such as lentils. The nature, as well as the amount, of protein in the diet had to be evaluated.

Vitamins were considered to be deficient when, for a long period of time, foods which are recognized to supply them were scant in the diet or rarely consumed. A patient was considered to have received little of vitamin C when fresh fruits and vegetables in small amounts and animal food, rich in vitamin C, were taken but once or twice a week. When there was any reasonable doubt as to whether the diet of a patient was grossly deficient in a given vitamin, the diet was classified as being on the borderline of deficiency.

TABLE 1—*Distribution of Subjects as to Sex, Age and Social Status*

	Number of Cases	Private Patients	Patients from Clinic	Sex		Age			Diet		
				Males	Females	Minimum	Maximum	Average	Borderline Deficient, per Cent of Cases	Deficient, per Cent of Cases	Undesirable, per Cent of Cases
Hypertrophic (degenerative) arthritis	27	11	16	5	22	40	78	56	7.4	25.9	33.3
Atrophic (rheumatoid) arthritis	40	12	28	11	29	18	60	35	37.5	12.5	50.0
Infectious arthritis	8	2	6	6	2	19	70	36	25.0	25.0	50.0
Control	30*	4	26	7	23	16	72	35	26.7	13.3	40.0
Total	105	29	76	29	76						

\* The number of private patients is relatively small in the control group. This may increase slightly the percentage of undesirable diet.

In evaluating the mineral content of the diet, only instances of gross inadequacy could be considered. The diet of one patient consisted of one serving of meat, three eggs, 1 pound (0.5 Kg.) of butter, seven moderate servings of oatmeal and three or four onions a week, in addition to potatoes, white bread, jam and cake. This diet was obviously inadequate in such minerals as iron and calcium.

The designation of a diet as undesirable depended on a summation of the various factors. A diet grossly lacking in any one or several of the essential constituents was said to be deficient.

Table 1 shows the distribution of the group of patients as to sex, age and, to an extent, social status, and table 2 is the form used for recording the dietary history. Each patient was questioned carefully about his dietary habits preceding the onset of the symptoms of disease of the joints. The diet recorded was, with few exceptions, that of the patient's lifetime habits, and care was taken to note any definite changes in the diet preceding the onset of arthritis. Indeed, in the seventy-five

TABLE 2—Chart Used in Recording Individual Dietary Habits

Name	Age	Sex	Diagnosis
Address			Date
Married	Years	Children	Hospital no
Present occupation			Height
Past occupation			Weight
Other activities			Av weight
			Cal normal weight
			+ or — av normal weight
			Now
			In past
Social status	Race	Birthplace	Lived in
Eats at home	In restaurant	Alone	Married
Does own cooking		Living conditions	
Emotional strain		Fatigue	
Rises	Retires	Naps	Sleeps well
Housework		Play	
Past history			
Arthritis began		Extent	Severity
Joints involved			
Family history			
Parents', brothers' and sisters' heights and weights			
Arthritis			
		Food Habits	
Typical day			
Breakfast			
Noon meal			
Evening meal			
Between meals			
Regularity	Likes	Appetite	Dislikes
Dieting		Seasonal variation	
Evidence of starch indigestion			
Tea	Coffee	Cream	Sugar
Alcohol	Tobacco		Condiments
Servings per week			
Meat	Butter	Bread (sliced) white	Ice cream
Fish	Cream	Bread (sliced) dark	Candy
Poultry	Mayonnaise	Crackers	Cake,
Eggs	Oleomargarine	Cereals (refined)	Pie
Cheese	Nuts	Cereals (whole)	Pudding
Liver	Lard	Potato	Pastry
Milk	Olive oil	Rice	Jams
	Macaroni		
Fruit (raw)		Lettuce	
Fruit (cooked)		Spinach	
Oranges		Cabbage	
Tomatoes		Carrots	
Vegetables (above ground)		String beans	
Vegetables (below ground)		Peas	
		Past Food Habits	
Childhood and youth			
Recent changes			
		Type of Diet	
Protein		Vitamins	
Fat		Minerals	
Carbohydrates		Calories	

patients with chronic arthritis, the diet recorded in the history represented the type of diet consumed for more than ten years in all but four instances. Similarly, it was found that but two patients of the control group had altered their diets essentially within a corresponding period. In evaluating the information obtained it was necessary to consider the diet of "a typical day," the weekly servings of the various food substances, the food habits, the occupation and the average body weight or changes in body weight while the diet was being taken. In addition, such factors as emotional strain and the habits of life, which may indirectly influence the food consumed, were taken into account.

At best it is possible to obtain only an approximation of the contents of diets from the patients' descriptions. The various constituents were classified as (1) in excess of an apparently desirable optimum, (2) the

TABLE 3—*Results of Study of Diet*

	Number of Cases	Carbohydrate Excessive, per Cent of Cases	Protein Inadequate, per Cent of Cases	Caloric Value		Vitamins		
				Excessive, per Cent of Cases	Inadequate, per Cent of Cases	Borderline, Deficient, per Cent of Cases	Deficient, per Cent of Cases	Total Deficient, per Cent of Cases
Hypertrophic (degenerative) arthritis	27	52	33	59.0	3.7	3.7	23.0	26.7
Atrophic (rheumatoid) arthritis	40	60	5.0	35.0	20.0	20.0	22.5	42.5
Infectious arthritis	8	75	0.0	37.5	12.5	12.5	37.5	50.0
Control	30	63	7.4	43.0	3.3	20.0	13.3	33.3
Total	105							

optimum, (3) borderline deficient and (4) deficient for the given person. The proportion of undesirable diets in all groups was surprisingly similar, as shown in table 1.

The duration and the extent of the arthritis were estimated at the time of examination. No correlation could be established between the adequacy of the diet and the duration and extent of the disease process. As was to be expected, the poorer diets in general were those of persons of obviously poor social status. However, poor diets were found in one fourth of the patients whose financial circumstances were good.

As a diet may be termed unsatisfactory in a number of ways, certain essential constituents and relationships were considered critically. Careful consideration was given to excess of carbohydrates, protein deficiency, total caloric content and vitamin and mineral content. The results of the study are recorded in table 3.

It can be seen that there was no striking single abnormality in the diets of any one group of patients with chronic arthritis. The percentage of patients who had for years consumed grossly excessive amounts of carbohydrate foodstuffs did not vary appreciably in any

group of patients with chronic arthritis or differ from that of the control group. Diets of caloric value excessive for the individual subject were encountered in a greater number of the patients with hypertrophic arthritis than in the other groups. It was expected that this would be the case, hypertrophic arthritis is recognized as occurring more frequently in patients who are overweight than underweight. Patients who had atrophic arthritis had been receiving diets of obviously inadequate caloric content in slightly larger numbers than the other groups. The percentage of patients with atrophic arthritis who took an insufficient amount of vitamins, whether of one or of several, over a number of years, was somewhat greater than in the other groups. However, when the vitamins were considered individually, it was obvious that no one vitamin was concerned. Indeed, as is usually the case in man when a deficiency of vitamins is found, there is a deficit of several vitamins rather than of only one. In considering the mineral constituents of the diet, calcium, phosphorus, iron, sodium, potassium and iodine received attention. Gross inadequacies of one or of several of these minerals were present in approximately one sixth of the patients. As with the vitamins, several minerals rather than one alone were present in insufficient quantities. The percentage of diets inadequate in minerals was not significantly greater in one group of patients than in another.

The rôle of certain dietary constituents in the etiology of arthritis may be approached in another manner. A few careful studies of the diets and diseases common to certain tribes and nationalities might cast light on the question. Muley<sup>1</sup> reported but few cases of chronic arthritis in Turkey, where the diet is low in protein and high in carbohydrates and vitamins. Orr and Gilks<sup>2</sup> made an interesting study of the diets of two African tribes. Rheumatoid arthritis is a common disease among members of the tribe whose diet consists chiefly of protein and fat and is rich in calcium salts. On the other hand, diseases of the joints are uncommon in the tribe whose dietary is poor in calcium and whose caloric needs were supplied in the main by carbohydrate substances. Deformities of the bone and the teeth were, however, seen in the latter tribe.

We are not concerned here with the question of the ability of the patient with chronic arthritis to absorb or to utilize the dietary carbohydrates.

Patients with chronic arthritis who are undernourished may show improvement with the establishment of better nutrition. This has been accomplished in many ways, by including a diet liberal in carbohydrate

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1 Muley, K. Ernährung in Ost und West, Ztschr f Ernähr **1** 361, 1931.

2 Orr, J. B., and Gilks, J. L. Studies of Nutrition. The Physique and Health of Two African Tribes, Medical Research Council, Spec Rep Ser 155, London, His Majesty's Stationery Office, 1931, p 82.

with or without the administration of insulin<sup>3</sup> The contention that a diet per se high in carbohydrate predisposes the subject to arthritis is not borne out by these studies Diets containing an excess of carbohydrate foodstuffs are not found in any greater number among persons known to have arthritis, as compared with a control group, than among patients with diabetes Chronic arthritis is uncommon in some tribes whose diet has been high in carbohydrates for generations

The various vitamins have likewise been incriminated Results of experiments on animals have suggested that a deficiency of several of the vitamins may be related to the susceptibility to and the defense against infection The recent observations of Rinehart and Mettier<sup>4</sup> have pointed out the occurrence of lesions of the joints in animals which were fed a diet deficient in vitamin C and in which an infection was induced The characteristics of the lesions observed by these workers are those occasionally seen in patients with scurvy, and are fundamentally different from those found in arthritis The presence of infection seems only to have increased the severity of the scorbutic process

On the basis of experiments on animals intestinal changes have been said to occur following a diet deficient in vitamin B<sup>5</sup> Fletcher<sup>6</sup> reported that the abnormalities of the intestine in patients with chronic arthritis change toward normal with the administration of vitamin B concentrates Haft,<sup>7</sup> in a carefully controlled study, concluded that the abnormalities of the intestines of patients with chronic arthritis were a manifestation of chronic illness and that they were not peculiar to this disease Nissen<sup>8</sup> would attribute colonic abnormalities in chronically ill patients, as seen in chronic arthritis and rheumatic heart disease, to a functional basis He observed improvement without alteration in the

3 (a) Howitt, F D, and Christie, W F The Malnutrition Factor in Rheumatoid Arthritis, *Lancet* **2** 1282, 1931 (b) Eaton, E R, and Love, J Chronic Arthritis A Study of the Dietary of Five Hundred Patients, with Results of an Experimental Course of Insulin Treatment in Twenty-Two Cases of Malnutrition, *J Am Inst Homeop* **26** 404 (June) 1933 (c) Dawson, M H Report of the Second Conference on Rheumatic Diseases, *J A M A* **101** 1264 (Oct 14) 1933

4 Rinehart, J F, and Mettier, S R The Joints in Experimental Scurvy and in Scurvy with Superimposed Infection, with a Consideration of the Possible Relation of Scurvy to Rheumatic Fever, *Am J Path* **9** 952 (Nov) 1933

5 McCarrison, R Studies in Deficiency Diseases, New York, Oxford University Press, 1921 Rowlands, M J Rheumatoid Arthritis Is It a Deficiency Disease? *Proc Roy Soc Med* **20** 1711 (May 25) 1927

6 Fletcher, A A Chronic Arthritis, *Canad M A J* **22** 320 (March) 1930

7 Haft, H H The Colonic Changes in Chronic Arthritis Compared with Other Chronic Diseases, *Am J M Sc* **185** 811 (June) 1933

8 Nissen, H A Atonic Stasis Clinical and Laboratory Study of Intestinal Variations in Chronic Disease, *M Clin North America* **13** 269 (July) 1929

vitamin allowance, but with the institution of muscle-building exercises and the addition of dietary roughage

Vitamin D has been thought to be lacking in patients with chronic arthritis. We have found no corroboration of this in our studies. Clinical improvement may follow the administration of generous amounts of this vitamin to individual patients, yet there seems to be no justification for a conclusion as to its specific value in arthritis.

While it has been suggested that long-continued, mild vitamin deficiency may be of etiologic importance in chronic arthritis, the infrequency of arthropathy in recognized diseases of vitamin deficiency in man speaks against this. Little evidence has been offered for any direct relationship between vitamin deficiency and chronic arthritis. On examination of the evidence at hand, it seems highly improbable that such a relationship will bear critical analysis.

The mineral content of the diet seems to have no part in the onset of chronic arthritis. The calcium salts have appeared to offer the most promising angle of approach. Studies of the calcium metabolism in patients with chronic arthritis have failed to offer any grounds for speculation in this field.<sup>9</sup> In the tribe whose members have received little calcium for years, bony and dental deformities are rather common, but disease of the joints is rare.

The observation of clinical alterations in patients following changes in the diet should hardly be interpreted as indicative of direct etiologic significance of the constituents involved. Eaton and Love<sup>3b</sup> have also concluded that there seems to be little or no direct evidence that diet or any of the various dietary constituents are directly contributory to the etiology of chronic arthritis. Dietary deficiency, in the broad sense, may decrease the powers of resistance to infections. Mackie and his associates<sup>10</sup> found evidence suggestive of this in experiments on animals. As in tuberculosis, it has been thought that predisposition to infection and impairment of the natural responses to infection accompany faulty food habits and undernutrition. Thus the importance of a proper diet in the treatment of arthritis is not lessened. In any chronic illness dietary therapy is recognized to be of great importance. No less so in

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9 Pemberton, R., and Foster, G. L. Studies on Arthritis in the Army Based on Four Hundred Cases. III. Studies on the Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, *Arch. Int. Med.* **25**: 243 (March) 1920. Bauer, W., Bennett, G. A., and Short, C. L. Speculations on the Etiology of Rheumatoid Arthritis, *New England J. Med.* **208**: 1035 (May 18) 1933.

10 Mackie, T. J., Fraser, A. H. H., Finkelstein, M. H., and Anderson, E. J. M. The Influence of Nutrition on Susceptibility to a Bacterial Toxin, *Brit. J. Exper. Path.* **13**: 323, 1932.

chronic arthritis is it essential to consider and to prescribe satisfactory diets, especially when altered intestinal function is present, as may be the case

There is, of course, no standard diet for patients with chronic arthritis or with any chronic illness. The object of a diet in chronic arthritis must be to attain the optimum nutrition in the individual patient. It is necessary to consider not only a satisfactory caloric intake, whether it is to be increased or decreased, but also ample protein, vitamins and minerals and the proper relationship of the constituents to each other. Various factors inherent to the patient must also be recognized. Related diseases and disorders, particularly of the gastro-intestinal tract, food idiosyncrasies, the patient's preferences, the appetite and the economic circumstances will necessitate due care on the part of the physician. It may be advisable for the patient to be reeducated with respect to his food habits.

#### SUMMARY AND CONCLUSIONS

The life dietary habits of seventy-five patients with chronic arthritis and thirty patients without symptoms in the joints were studied. Fifty-nine per cent of the patients with hypertrophic degenerative arthritis had had an excess of calories in their diet for years. This is in contrast to 43 per cent of the patients of the control group. Diets of inadequate caloric content were found in 20 per cent of the patients with atrophic (rheumatoid) arthritis, as compared with 3 per cent of the control group.

Undesirable diets were encountered in the cases of one third of the patients with hypertrophic arthritis and one half of the patients with atrophic arthritis. However, the diets of 40 per cent of a control group of patients of similar ages, sex and social status were likewise poor.

No direct relationship can be established between dietary factors and the development of chronic arthritis. Neither excessive consumption of carbohydrate nor a deficiency of the various vitamins and minerals per se was found to be related to the development of chronic arthritis. The importance, however, of a good diet in the treatment of chronic arthritis, as in the treatment of any disease state, is beyond question. The diet must fit the needs of the individual patient.

# THE UREA RATIO AS A MEASURE OF RENAL FUNCTION

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Tests for renal function are of two types—those that determine the power of the kidney to dilute and concentrate the urine and those that measure the ability of the kidney to eliminate the renal excretory products. Those of the first group, which includes the various tests for specific gravity, are well established and adequate, those of the second are not completely satisfactory. Beside the use of the dye tests, which are not specific, the measure of renal excretion usually is attempted by a determination of the amount of urea or nonprotein nitrogen in the blood. These estimations demonstrate how much of these substances is actually retained, but not the degree of the impairment of renal function. This is especially true when the figures for the blood chemistry determinations are low, it is not then certain whether renal function is normal or impaired, since the level of the nonprotein nitrogen in the blood may have been influenced by therapeutic measures, such as diet, or by complications, such as edema or diarrhea.

In 1917, Mosenthal and Hiller<sup>1</sup> suggested the ratio of the urea nitrogen to the nonprotein nitrogen of the blood as an index of the amount of effectively functioning renal tissue, irrespective of the level of the blood urea. Since that time, the methods for the determination of the nonprotein nitrogen have changed, observations are presented here on the validity of the urea ratio as a test for renal function when the more recent quantitative procedures are employed.

The urea clearance test of Van Slyke<sup>2</sup> and his collaborators has proved to be the most satisfactory method now available for the per-

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1 Mosenthal, H. O., and Hiller, A. The Relation of the Nonprotein Nitrogen to the Urea Nitrogen of the Blood, *J. Urol.* **1** 74, 1917

2 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6** 427, 1928

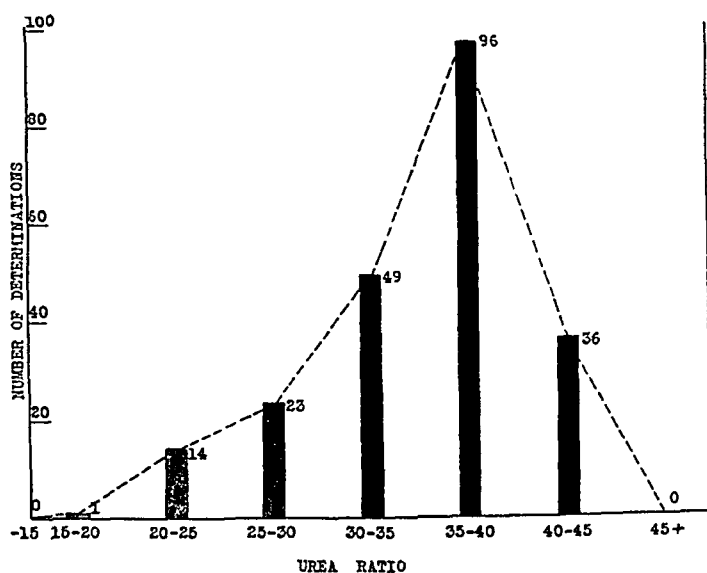


centage estimation of the total active renal tissue. Consequently the urea ratio has been checked by comparison with the urea clearance values in many of these observations.

#### MATERIAL AND METHODS

Since 1931 more than 1,500 determinations of the urea nitrogen and the total nonprotein nitrogen in the whole blood have been carried out simultaneously on 307 persons. The patients were studied consecutively as they presented themselves in the wards and clinics of the New York Post-Graduate Hospital, in the metabolic wards of Sea View Hospital, Staten Island, and in the private practice of one of us (H O M). The patients studied were grouped as follows:

1 Persons with normal renal function (laboratory workers, interns and patients with nonrenal diseases, for example, diabetes mellitus or peptic ulcer)—200 patients



Distribution of 219 determinations of the urea ratio in 200 persons with normal renal function. The minimum urea ratio is 16.1, the maximum, 43.3.

2 Patients with Bright's disease (acute diffuse glomerular nephritis, chronic diffuse glomerular nephritis, with or without nephrotic components or uremia, focal embolic nephritis, lipid nephrosis, amyloid nephrosis, or arteriosclerotic nephritis)—92 patients

3 A miscellaneous group of patients with impaired renal function (surgical diseases of the kidney, for example, prostatic obstruction and renal lithiasis, chronic passive congestion due to cardiac decompensation, and dyscrasias of the blood, such as agranulocytosis, leukemia and polycythemia vera)—15 patients

In every instance, the urea nitrogen in the whole blood was determined on the Folin-Wu filtrate by Van Slyke's gasometric urease method,<sup>3</sup> and the total non-protein nitrogen, by the method of Folin and Wu.<sup>4</sup> The urea clearance test was

3 Van Slyke, D. D. Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease, *J Biol Chem* **73** 695, 1927.

4 Folin, O., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919.

carried out according to the procedure of Moller, McIntosh and Van Slyke<sup>2</sup> The percentage of urea nitrogen in the total nonprotein nitrogen of the blood, termed the urea ratio, was calculated according to the formula  $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$

## RESULTS

*Normal Value of the Urea Ratio*—In 219 determinations of the urea ratio in the blood of 200 persons with normal renal function (chart), only 1 ratio was lower than 20, the highest observed was 43.3. In the 219 observations, 145 urea ratios were between 30 and 40, indicating clearly that this was the usual figure. For practical clinical interpretations, we have considered as normal urea ratios of 44 or less.

TABLE 1—*The Urea Ratio and Urea Clearance Values in Persons with Normal Renal Function*

No	Patient	Whole Blood		Urea Ratio	Urea Clearance, per Cent of Normal
		Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc		
1	Bas	5.0	24.5	20.4	148.9
2	Dis	6.1	22.7	26.9	84.8
3	Bas	7.1	30.0	23.7	125.4
4	Bas	7.1	33.2	21.4	107.5
5	Bas	7.3	29.3	24.9	119.7
6	Han	7.6	30.0	25.3	151.8
7	Car	8.2	27.7	29.6	99.1
8	Car	8.7	29.3	29.7	97.3
9	Hun	8.7	29.3	29.7	100.5
10	Han	8.7	28.2	30.9	177.3
11	Car	9.1	26.7	34.1	89.9
12	Hun	9.1	27.6	33.0	115.2
13	Hun	9.1	29.5	30.9	94.1
14	Hun	9.4	26.9	34.9	89.5
15	Han	9.4	26.8	35.1	176.8
16	Han	9.7	30.3	32.0	150.9
17	Han	9.8	33.3	29.4	108.1
18	Kla	9.9	35.1	28.2	119.6
19	Han	10.0	30.5	32.8	103.3
20	Gro	10.1	25.2	40.1	141.8
21	Kla	10.1	27.3	37.0	135.2
22	Kla	10.6	31.4	33.8	107.6
23	Law	10.9	30.6	35.6	74.8
24	Bla	11.3	28.0	40.4	83.3
25	Sch	13.8	37.3	37.0	86.8
26	Osn	15.4	35.6	43.3	111.2
27	Sho	16.9	40.0	42.3	81.0

Table 1 compares the urea ratio and the urea clearance value in persons with normal renal function. The results of the two tests in this group are in entire agreement. The tendency toward a low urea ratio when the blood urea is considerably depressed is evident. This apparently is characteristic of normal persons, though it does not hold true, as will be shown later, in those with diminished renal function, in whom a low urea nitrogen is accompanied by a constantly elevated urea ratio irrespective of the fluctuations in the urea nitrogen of the blood.

*The Urea Ratio with Maximal Impairment of Renal Function*—When renal activity is curtailed to the utmost, the urea ratio is usually at a level of 80 or more. This is shown in table 2, which gives the

urea ratio in 16 cases of chronic diffuse glomerular nephritis with uremic manifestations. It appears that a urea ratio of 80 indicates a maximal impairment of renal function though a higher ratio (in one instance in this series 91.9 table 2) may be reached.

TABLE 2—*The Maximum and Minimum Urea Ratios Observed in Sixteen Patients with Chronic Diffuse Glomerular Nephritis with Uremic Manifestations*

No	Patient	Number of Ratios Obtained	Whole Blood Urea Nitrogen, Mg per 100 Cc		Urea Ratio	
			Maximum	Minimum	Maximum	Minimum
1	Car	2	113.5	111.1	90.4	88.0
2	Sag	6	118.0	101.5	85.1	75.6
3	Rlz	2	118.0	112.4	89.0	80.1
4	Roc	2	125.4	111.6	79.2	77.6
5	Flo	3	130.1	95.4	83.8	73.2
6	Tar	2	135.2	105.8	84.5	80.4
7	Sab	6	135.3	116.0	87.9	77.0
8	Ham	5	170.3	139.0	91.9	81.2
9	Ell	4	171.0	153.7	91.4	82.6
10	Gli	19	173.7	109.3	90.6	78.6
11	She	3	180.2	156.8	82.1	78.7
12	Umm	2	180.9	147.5	83.5	77.9
13	Per	2	198.9	114.8	86.4	80.2
14	Kos	3	209.2	194.5	88.9	80.9
15	Got	2	231.6	194.9	72.1	68.2
16	Ang	5	275.7	218.5	75.3	67.4

TABLE 3—*The Urea Ratios in a Patient Aged 25, with Chronic Diffuse Glomerular Nephritis in a Preuremic State Over a Period of Seven Months, Showing the Rather Constant Maintenance of the High Ratio in Spite of the Variations That Occur in the Nonprotein Nitrogen of the Blood as the Result of Treatment*

Date	Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Urea Ratio	Date	Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Urea Ratio
1933				1933			
Feb 4	85.7	111.1	77.1	Feb 23	50.8	69.0	73.6
Feb 8	80.5	93.0	86.6	Feb 28	58.2	78.4	74.2
Feb 9	80.2	90.5	88.6	March 4	60.9	85.1	71.6
Feb 10	74.2	81.3	91.3	March 10	80.8	90.5	89.3
Feb 11 a m	71.5	82.6	86.6	March 13	69.9	90.2	77.5
Feb 11 p m	69.1	82.3	84.0	March 14	68.6	90.9	75.5
Feb 12	67.4	75.2	89.6	March 15	63.5	90.9	69.9
Feb 15	65.6	73.3	89.5	March 20	50.2	83.9	59.8
Feb 16	67.1	85.8	78.2	March 28	51.0	69.8	73.1
Feb 17	64.8	83.3	77.8	April 11	51.6	84.5	61.1
Feb 18	63.1	83.3	75.8	April 27	89.9	110.5	81.4
Feb 20 a m	59.7	78.4	76.1	Aug 16	139.0	170.4	81.6
Feb 20 p m	61.9	83.9	73.8	Sept 2	170.3	185.3	91.9
Feb 21	50.3	82.7	71.7	Sept 5	163.4	197.4	82.8

In table 3 are tabulated the urea ratios in a patient with chronic diffuse glomerular nephritis who was in a preuremic state for seven months. Although the ratio was frequently 80 or above, some lower figures are shown. Presumably the efficiency of the kidney may vary according to the amount of fluid intake, the volume of urine eliminated and other factors. These may well be responsible for certain fluctuations in the urea ratio pictured in a series of determinations of this sort.

*Fluctuations in the Urea Ratio as the Result of Changes in Renal Function*—Changes in the urea ratio may occur in either an upward or a downward direction, marking a diminution or an improvement in renal efficiency. In table 4 are given the urea ratios in 4 patients with acute nephritis in whom a complete or partial functional recovery took place. The urea ratio reaches the normal level in the first 3 patients and approaches it in the fourth, indicating either complete recovery or a

TABLE 4—*The Urea Ratios in Four Patients with Acute Diffuse Glomerular Nephritis with Complete or Partial Functional Recovery, Showing a Drop in the Ratio which Occurs to a Large Extent In irrespective of the Values of the Blood Urea Nitrogen*

Date, 1933	Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Urea Ratio	Comment
Patient Ban, age 10				
April 10	110.3	119.6	92.2	Acute diffuse glomerular nephritis, marked impairment of renal function
April 11	93.6	118.9	78.7	
April 13	40.6	48.4	83.9	
April 17	17.6	30.9	57.0	
April 22	14.1	37.7	37.4	Complete functional recovery
Patient Laz, age 28				
Feb 7	19.5	31.9	61.1	Acute diffuse glomerular nephritis with nephrotic component, considerable impairment of renal function
Feb 16	30.2	47.3	63.9	Urea clearance 28.2 per cent of normal
Feb 24	20.2	35.1	57.6	
March 7	38.8	49.2	78.9	Urea clearance 45.8 per cent of normal
March 29	24.4	38.5	63.4	
Aug 9	10.3	28.3	36.4	Complete functional recovery
Patient Fif, age 22				
Feb 6	37.1	56.1	66.1	Acute diffuse glomerular nephritis, considerable impairment of renal function
Feb 12	27.0	37.1	72.8	Urea clearance 32 per cent of normal
Feb 20	18.2	33.8	53.9	
Feb 28	14.9	26.2	56.9	Urea clearance 45.5 per cent of normal
March 7	12.0	23.1	52.0	Urea clearance 66.1 per cent of normal, complete functional recovery
March 21	8.6	25.4	33.9	
April 18	7.6	25.4	29.9	Urea clearance 98 per cent of normal
June 15	7.9	30.9	25.6	
Sept 1	10.2	28.8	35.4	
Patient Riz, age 40 1932				
Nov 2	118.0	147.2	80.2	Acute exacerbation of chronic diffuse glomerular nephritis
Nov 5	112.4	126.2	89.1	
Nov 7	86.2	103.6	83.2	
Nov 9	42.8	52.0	82.3	
Nov 15	14.6	27.0	54.1	Urea clearance 53.6 per cent of normal
Nov 16	14.1	24.7	57.1	Partial functional recovery

distinct improvement in the renal function, the urea ratio thus furnishes a good numerical index of the sequence of events. It is strikingly evident from this table that in many instances determinations of either the urea nitrogen or the total nonprotein nitrogen do not indicate the existence of any impairment of renal function, on the other hand, the urea ratio shows that a definite degree of renal impairment exists in the face of normal values for these constituents.

Table 5 shows how the urea ratio rises as impairment of renal function progresses over a period of almost two years. Here, the urea ratio furnishes an index of the extent of curtailment in the activity of the kidney.

*Comparison of the Urea Ratio with the Urea Clearance*—The figures in table 6 are those from simultaneous determinations of the urea ratio and urea clearance in the blood of patients with Bright's disease. The cases are arranged in order of the diminishing values of urea clearance. In general, the urea ratio rises as the urea clearance value falls. While the results of the two tests are usually in agreement, they do not entirely parallel each other. It may be that each measures a somewhat different quality in renal function from that shown by the other and, consequently, the results are not always in absolute accord. However, the discrepan-

TABLE 5—*Rise of the Urea Ratio During a Period of Almost Two Years in a Patient Aged 25, with Chronic Diffuse Glomerular Nephritis, Who Died of Retention Uremia*

Date, 1930	Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Urea Ratio	Urea Clearance, per Cent of Normal
Dec 22	18.5	38.9	47.6	26.2
1931				
Jan 7	21.7	41.6	52.2	40.2
March 20	22.0	42.5	51.8	28.8
March 28	26.6	40.0	66.5	29.7
1932				
April 18	84.7	110.4	76.7	9.0
May 31	109.0	155.4	70.1	
June 3	107.1	137.0	78.2	
June 7	81.7	124.2	65.8	
June 14	93.3	116.2	80.3	
Sept 8	111.7	157.9	70.7	
Sept 29	153.7	186.0	82.6	
Sept 30	164.2	186.8	87.9	
Oct 2, a. m.	171.0	203.2	83.3	
Oct 2, p. m.	170.8	186.8	91.4	
Oct 3, exitus				

cies between the two tests are so slight as to make it certain that if one is of value the other must be satisfactory.

In some instances (cases 1, 2 and 3, table 6) the urea ratio indicates impairment of renal function whereas the value for urea clearance does not. At times, there are fluctuations in the urea ratio, which are noted in table 3 and have been discussed. Similar variations may be observed in the urea clearance values in table 5. We previously had an identical experience with this procedure.<sup>5</sup> The same explanation may be offered for these variations as for those in the urea ratio. Neither of the tests furnishes entirely constant results, and the changes in their results from time to time may be due to alterations in the activity of the kidney.

5 Bruger, M., and Mosenthal, H. O. Urea Clearance Test as an Index of Renal Function. III. Studies of Patients with Bright's Disease, Arch Int Med 50:544 (Oct) 1932.

*Urea Ratio in Conditions Other Than Bright's Disease*—With mechanical obstruction to the urinary flow (renal calculus or prostatic

TABLE 6—*Simultaneous Determinations of the Urea Ratio and Urea Clearance Values in Patients with Bright's Disease*

No	Patient	Whole Blood		Urea Ratio	Urea Clearance, per Cent of Normal	Type of Bright's Disease*
		Urea Nitrogen, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc			
1	Wal	17.4	29.4	59.2	100.7	2
2	Ris	14.4	29.8	48.3	88.1	2
3	Fri	14.4	31.1	46.3	81.3	2
4	Ste	16.2	33.1	48.9	65.1	2
5	Law	12.1	25.7	47.1	64.0	5
6	Fin	18.7	32.9	56.8	55.3	2
7	Rlz	14.6	27.0	54.1	53.6	2B
8	Kro	26.9	50.4	53.4	49.6	5
9	Laz	24.4	38.5	63.4	45.8	2B
10	Lev	20.6	39.7	51.9	45.7	2
11	Fif	14.9	26.2	56.9	45.5	1
12	Nus	19.5	40.7	47.9	45.2	2A
13	Nus	24.9	51.7	48.2	42.1	2A
14	Nus	19.7	38.6	51.0	41.8	2A
15	Ell	21.7	41.6	52.2	40.2	2A
16	Kro	22.6	36.9	61.3	39.2	5
17	Lev	22.8	41.9	54.4	36.2	2
18	Har	20.6	35.1	58.7	36.1	5
19	Lev	20.1	40.8	49.3	35.1	2
20	Gli	27.9	41.1	67.9	34.4	2
21	Fad	21.4	38.2	56.0	32.3	2
22	Fif	18.2	33.8	53.9	32.0	1
23	Ell	26.6	40.0	66.5	29.7	2A
24	Ell	22.0	42.5	51.8	28.8	2A
25	Laz	20.2	35.1	57.6	28.2	2B
26	Roe	40.3	48.6	82.9	26.5	3
27	Ell	18.5	38.9	47.6	26.2	2A
28	Ros	33.4	56.6	59.0	26.0	2
29	Nat	33.8	45.8	73.8	24.8	2
30	Gli	31.8	57.2	55.6	24.2	2
31	Ros	35.4	56.3	62.9	23.3	2
32	Ros	35.3	55.1	64.1	23.3	2
33	Duf	29.7	40.7	73.0	20.9	4
34	Leo	43.2	71.4	60.5	18.8	2A
35	Ros	44.0	56.3	78.1	18.7	2
36	Leo	31.0	41.7	74.3	18.6	2A
37	Gee	23.0	50.0	56.0	18.5	2A
38	Byr	53.5	81.6	65.6	15.2	2
39	Ros	51.4	72.7	70.7	14.5	2
40	Nat	31.7	43.8	72.4	13.9	2
41	Gee	46.0	70.6	65.2	12.8	2A
42	Gee	74.1	117.6	63.0	12.5	2A
43	Sho	58.8	76.9	76.5	11.6	2
44	Nus	95.8	131.2	73.0	10.5	2A
45	Ell	84.7	110.4	76.7	9.0	2A
46	Fis	114.0	136.0	83.8	7.4	2C
47	Sag	104.0	127.6	81.5	7.1	2C
48	Sag	76.3	120.0	63.6	6.2	2C
49	Wit	62.8	94.2	66.7	6.1	2
50	Gli	167.1	222.2	75.2	4.8	2
51	Gol	166.6	253.5	65.7	4.4	2C
52	Gos	209.2	235.2	88.9	4.4	2C
53	Eck	69.8	97.8	71.4	4.3	2C
54	Sab	131.4	154.7	84.9	3.8	2
55	Sab	128.6	147.0	87.5	3.0	2

\* 1 indicates acute diffuse glomerular nephritis, 2, chronic diffuse glomerular nephritis, including that with (A) a nephrotic component, (B) an acute exacerbation of chronic diffuse glomerular nephritis, or (C) uremic manifestations, 3, focal embolic nephritis, and 4, amyloid nephrosis

obstruction), the urea ratio was observed to be elevated when impairment of renal function was present. In patients with dyscrasias of the blood (agranulocytosis, polycythemia vera or leukemia), the urea ratio

was high. This may be due to an excessive destruction of the blood cells and a consequent increase in the urea within the blood stream. The renal insufficiency incidental to passive congestion was accompanied by an increase above the normal in the urea ratio. Patients with diseases of the liver showed a very low urea ratio. Nepveux and Hiernaux,<sup>6</sup> in 1927, called attention to this and ascribed it to the diminished activity of the liver in forming urea from the amino-acids in the blood.

#### COMMENT

Nepveux and Hiernaux,<sup>6</sup> in 1927, pointed out that Schondorff and Strauss in Germany and Widal and Rouchese, in 1906, in France were the first to study the "azotemic ratio," or, as we have termed it, the urea ratio. There has apparently been a lack of agreement on the significance of the ratio because of the widely different methods employed for the determination of the urea nitrogen and the total nonprotein nitrogen. Nepveux and Hiernaux noted that the urea ratio increases as the urea is retained in the blood in cases of Bright's disease. Mosenthal and Hiller,<sup>1</sup> in 1917, reported results identical with those given in this paper, except that their ratio was at a higher level because of the different chemical methods in vogue at that time for the determination of the total nonprotein nitrogen of the blood.

It is admitted that the concentrations of uric acid, creatinine and, at times, amino-acids and other forms of nitrogen rise in the blood as renal insufficiency develops, however, the urea nitrogen of the blood increases faster than the total amount of nitrogen contained in these substances and, consequently, the urea ratio is elevated when renal function is impaired. An interesting point, and one that is of great importance in using the urea ratio as a test for renal function, is that it remains approximately constant no matter how the level of the nonprotein nitrogen of the blood is modified by diet or complications, such as vomiting and diarrhea. In other words, the urea ratio reflects the efficiency of the kidney, irrespective of the actual urea values of the blood.

The normal kidney is able to concentrate urea to a greater extent than any of the other nitrogenous derivatives of protein catabolism, with the exception of creatinine. For this reason, the partition of the nonprotein nitrogen in the blood and urine is not equal, the urea nitrogen, as has already been seen, constituting approximately 40 per cent of the total nonprotein nitrogen in normal laked blood (60 per cent in normal

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<sup>6</sup> Nepveux, F., and Hiernaux, A. Valeur du rapport azotémique, *Médecine* 8 757 (July) 1927.

unlaked blood<sup>7</sup>) and 80 per cent or more in the urine<sup>8</sup>. With the presence of a slight or moderate degree of renal insufficiency, the selective concentration of urea by the kidney is impaired. The result is that, even though no obvious retention of nitrogen in the blood takes place, there is a relative retention of nitrogen, and the ratio of urea nitrogen to the total nonprotein nitrogen is increased.

#### SUMMARY AND CONCLUSIONS

The urea ratio expressed as the percentage of urea nitrogen in the total nonprotein nitrogen in the blood, or  $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$  is a satisfactory index of renal efficiency. When the Folin-Wu filtrate (laked blood) is used for the determination both of the urea nitrogen and of the total nonprotein nitrogen in the blood, it is noted that the urea ratio varies with renal function as follows:

(A) with normal renal function, an index of 44 or less, (B) with maximal impairment of renal function, an index of 80 or higher, (C) with improvement in renal function, a drop in the ratio, and with progressive impairment of function, a rise in the ratio.

The determination of the urea ratio at intervals measures progressive changes in renal efficiency and affords a reliable index of renal function, regardless of the fluctuations of the total nonprotein nitrogen of the blood. Although the urea nitrogen or the total nonprotein nitrogen in the blood may be at a normal level, the urea ratio reveals renal insufficiency when it exists. This test may be carried out on one specimen of blood, it does not require prolonged observation of the patient or collection of urine. It furnishes a numerical index of the degree of impairment of renal function and is equally applicable to patients in private practice and to those in the hospitals.

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7 Folin, O., and Svedberg, A. Diffusible Nonprotein Constituents of Blood and Their Distribution Between Plasma and Corpuscles, *J. Biol. Chem.* **88**: 715, 1930.

8 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 272.



# THERMAL STUDY OF VASOMOTOR LABILITY IN PREGNANCY

## PRELIMINARY REPORT

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That vascular tension is an important factor in the mechanism of the toxemias of pregnancy was postulated many years ago Cohnheim,<sup>1</sup> in 1880, seems to have been the first to express the view that albuminuria and anuria in eclampsia might be due to a spasm of the renal vessels. In 1918, Volhard<sup>2</sup> advanced the hypothesis that a generalized arterial spasm accounted for the hypertension, convulsions and renal symptoms in eclampsia. Heynemann<sup>3</sup> also assumed that a general arterial spasm produced the symptoms. Various attempts to demonstrate vascular spasm have been more or less successful. Hinselmann<sup>4</sup> (1924) noted the capillary changes in the finger-nail beds. He assumed that the capillary stasis and the dilatation were secondary to an arteriolar spasm. Subsequent observations of the nicking of retinal arteries and veins and the beading and the contractions of these vessels have indicated that the vascular spasm is probably general.

To our knowledge, no extensive studies of vascular tension in pregnancy have been made. Clinically, Adair<sup>5</sup> and deSnoo<sup>6</sup> have shown that essential hypertension is the characteristic feature of many cases of toxemia of pregnancy. Since vasomotor lability may be used as an index of vascular tension, we sought a simple method whereby the lability could be determined with reasonable accuracy. Klyn<sup>7</sup> (1926) emphasized the observations of Kaufman (1924) that patients

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From the Department of Obstetrics and Gynecology, the University of Chicago, and the Chicago Lying-In Hospital

1 Cohnheim, J. Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880

2 Volhard, F. Die doppelseitigen haematogenen Nierenerkrankungen (Brighl'sche Krankheit), Berlin, Julius Springer, 1918

3 Heynemann, quoted by Fahr, in Hinselmann<sup>4</sup>

4 Hinselmann, H. Die Eklampsie, Bonn, F. Cohen, 1924

5 Adair, F. L. Analysis of a Series of Nonconvulsive Cases of Toxemias of Pregnancy, Am J Obst & Gynec **26** 530 (Oct) 1933

6 deSnoo, K. Blood Pressure in the Pregnant, Monatschr f Geburtsh u Gynak **57** 235 (April) 1922

7 Klyn, E. Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926

with hypertension showed a response to changes in external temperature that was different from that of normal persons. Stieglitz<sup>8</sup> called attention to the work of Hines and Brown,<sup>9</sup> who demonstrated that the vasomotor responses to the stimulus of cold water (4 or 5 C) were apparently specific. These authors found that patients with primary hypertension and normal subjects with a family history of hypertension (prehypertension) gave higher responses to such a stimulus than did normal subjects with no family history of hypertension.

#### TECHNIC

The subject was placed in a comfortable chair or in a semireclining position in bed. All extraneous noises and distractions were reduced to a minimum. A preliminary period of rest lasted for from fifteen to thirty minutes. A blood pressure cuff was then applied to the arm, and the apparatus was raised to the cardiac level. An arm-band stethoscope was then adjusted to the cubital fossa, and the subject was permitted another short period of rest. From three to ten readings were taken at intervals of from five to ten minutes until a basal reading was obtained. The stimulus consisted of cold water, the temperature being approximately 1 C. This temperature was obtained by mixing chipped ice and water in a basin and immersing therein the extended hand of the arm bearing the blood pressure cuff until the ice-water reached the wrist. Blood pressure readings were taken immediately and then every thirty seconds for two minutes. After the test the hand was gently dried and another series of readings was taken at intervals of thirty seconds in order to determine the length of time required for the blood pressure to approach the basal level.

#### OBSERVATIONS

One hundred and ninety women were studied. They were divided into two groups—the pregnant and the nonpregnant. Whenever possible, an attempt was made to obtain an accurate family history of hypertension. The pregnant patients were grouped as follows: normal, preeclamptic, eclamptic and having chronic nephritis. The preeclamptic group was composed of primiparas who had edema, hypertension and albuminuria and usually other symptoms, such as diplopia, dizziness, headaches, oliguria, etc. The onset of the toxemia occurred in the last six or eight weeks of pregnancy. The eclamptic group differed in that the patients, in addition, had convulsions and/or coma. The group with chronic nephritis was composed of the remainder of the patients and included those with primary hypertension, chronic glomerulonephritis and a recurrence of toxemia. The observations were carried out at prolonged intervals, and as many as eight tests were made on some patients.

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8 Stieglitz, E. J. Personal communication.

9 Hines, E. A., Jr., and Brown, G. E. Standard Stimulus for Measuring Vasomotor Reactions. Its Application in the Study of Hypertension, Proc. Staff Meet., Mayo Clin. 7:332 (June 8) 1932.

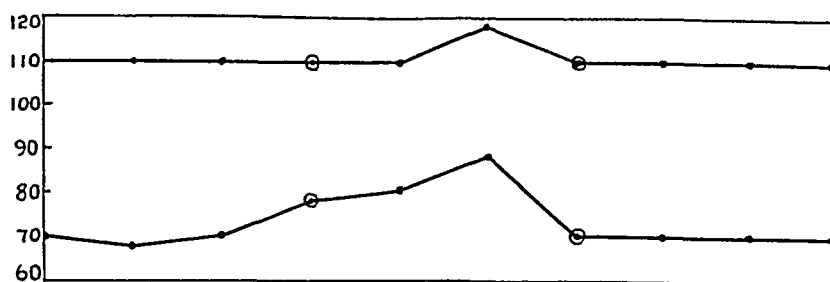


Fig 1—Typical graph of the blood pressure of nonpregnant women without a family history of hypertension

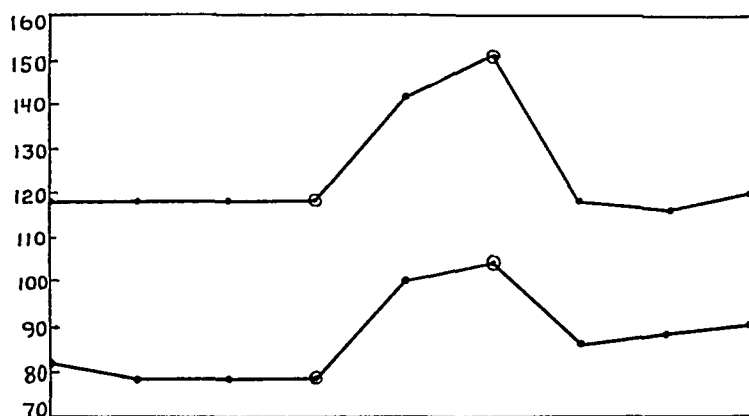


Fig 2—Typical graph of the blood pressure of nonpregnant women with a family history of hypertension

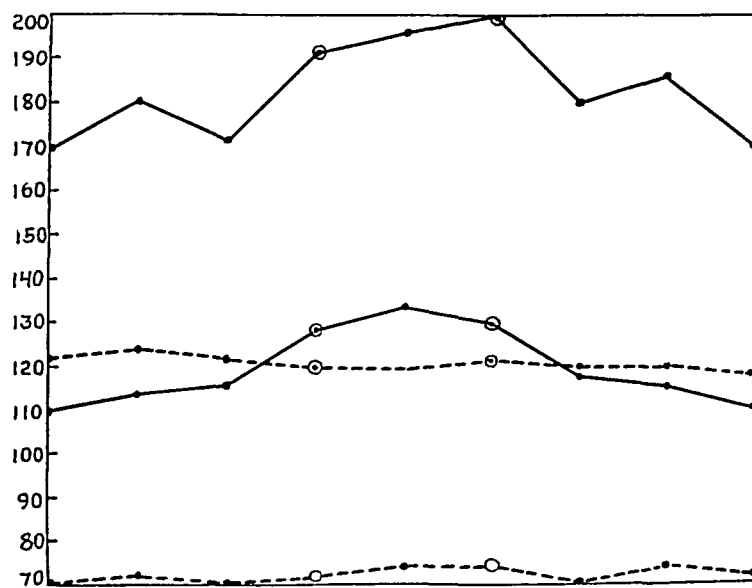


Fig 3—Typical graph of the blood pressure of a preeclamptic patient in the antepartum and postpartum periods. In figures 3 to 5 the solid lines represent the readings before delivery, the dotted lines, the readings after delivery

In a group of twenty-eight nonpregnant subjects with a family history of hypertension, the mean rise in blood pressure was 35.07 mm of mercury systolic and 34.5 mm diastolic. In forty-two nonpregnant

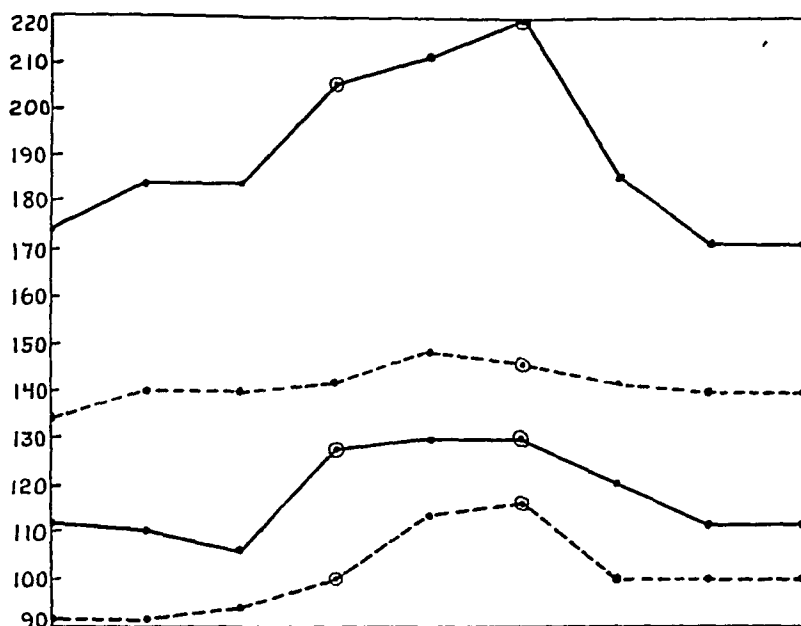


Fig 4—Typical graph of the blood pressure of an eclamptic patient in the antepartum and postpartum periods

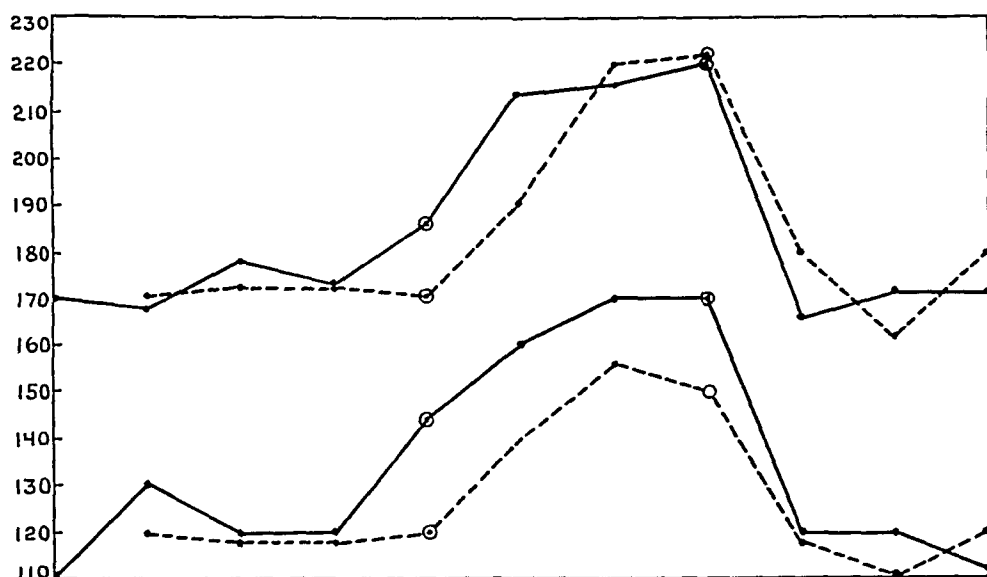


Fig 5—Typical graph of the blood pressure of a patient with clinical nephritis in the antepartum and postpartum periods

women giving no definite family history of hypertension the mean rise was 18.76 mm systolic and 23.3 mm diastolic. Six patients with essential hypertension showed an increase of 36 mm systolic and 36 mm diastolic. In another group of six patients with symptoms of

vasomotor instability and no family history of hypertension, the average increase was 37 mm systolic and 35.3 mm diastolic.

In eighteen normal pregnant women without a family history of hypertension the mean antepartum rise was 19.56 mm systolic and 19.8 mm diastolic, and the postpartum rise was 15.11 mm systolic and 22 mm diastolic. In contrast, in thirteen normal pregnant women with a family history of hypertension the mean antepartum increase was

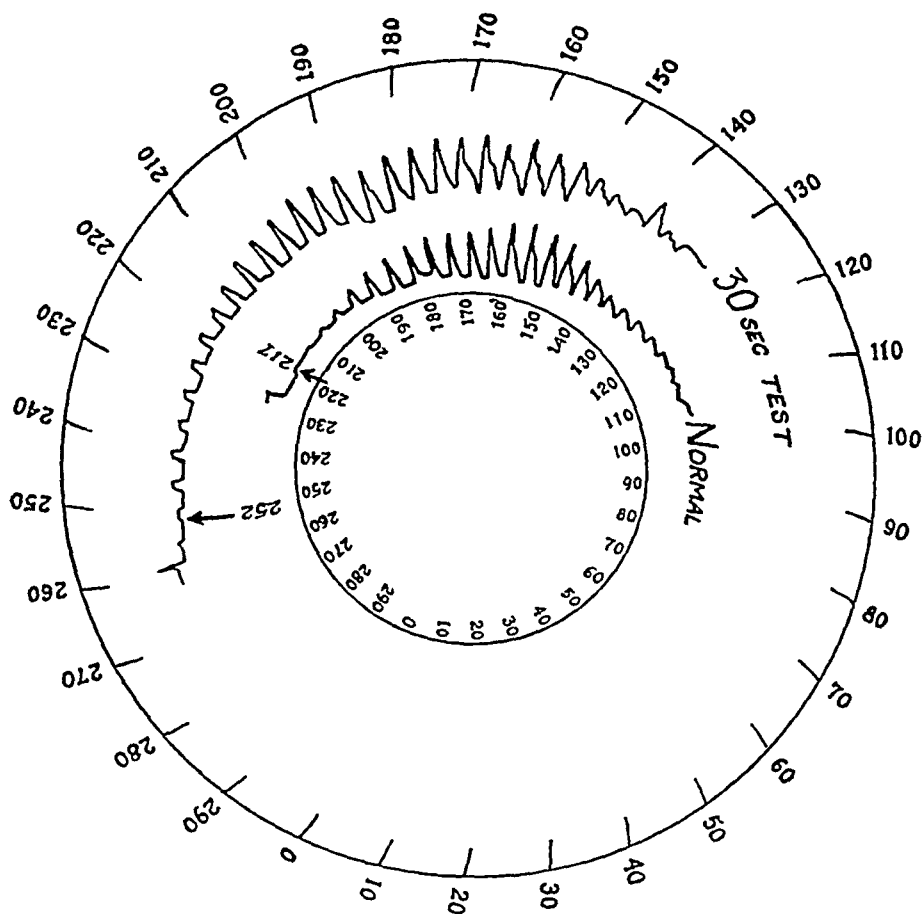


Fig 6—A graph obtained with a Tyco self-recording sphygmomanometer. *Normal* shows the basal reading before the application of ice-water. The adjacent graph was obtained thirty seconds after immersion of the hand in ice-water.

35.54 mm systolic and 26.1 mm diastolic, the postpartum rise was 39 mm systolic and 34 mm diastolic.

In the preeclamptic group the mean antepartum increase was 26.06 mm systolic and 23.6 mm diastolic, as compared with the postpartum rise of 26 mm systolic and 15.3 mm diastolic.

Five patients with eclampsia showed a mean antepartum increase of 26 mm systolic and 16.7 mm diastolic.

In thirty-three patients who were designated clinically as having chronic nephritis, the mean antepartum rise was 51.88 mm systolic and 37.5 mm diastolic, as compared to the postpartum rise of 51 mm systolic and 35.8 diastolic.

TABLE 1—*Fluctuations in the Systolic Blood Pressure Caused by a Standard Stimulus\**

Increase in Systolic Pressure, Mm. Mercury	Normal Nonpregnant Patients		Pregnant Patients			
	Family History of Hyper- tension	No His- tory of Hyper- tension	Family History of Hypertension		No History of Hypertension	
			Ante Partum	Post Partum	Ante Partum	Post Partum
0 to 9		4			5	2
10 to 19	1	15			3	4
20 to 29	5	20	4		6	3
30 to 39	15	3	6	3	3	
40 to 49	4		1	3	1	
50 to 59	3		1			
60 to 69			1			
Total number of patients	28	42	13	6	18	9
Mean increase in systolic pres- sure	35.07	18.76	35.54	39.0	19.56	15.11
S. D.	9.43	8.97	11.74	7.07	12.92	7.46
P. E.	1.2	0.93	2.2	1.95	2.05	1.68

\* In this table one notes a significant difference in the response between those subjects who gave a family history of hypertension and those who did not, irrespective of the presence of pregnancy. In tables 1 and 2 S. D. indicates standard deviation, P. E., probable error.

TABLE 2—*Fluctuations in the Systolic Blood Pressure in Toxemic Patients with Hypertension\**

Increase in Systolic Pressure, Mm. Mercury	Nephritic Toxemia		Preeclampsia		Eclampsia	
	Ante Partum	Post Partum	Ante Partum	Post Partum	Ante Partum	Post Partum
0 to 9				1	1	
10 to 19			7	8	1	2
20 to 29			16	17	1	2
30 to 39	4	6	9	11		
40 to 49	14	1	1	2	2	1
50 to 59	6	8	1	1		
60 to 69	5	4				
70 to 79	2					
80 to 89	2	1				
Total number of patients	33	20	34	40	5	5
Mean increase in systolic pres- sure	51.88	51	26.06	26	26.0	
S. D.	25.21	13.78	9.22	10	16.13	
P. E.	2.84	0.84	1.07	1.07	4.86	

\* This table represents a comparative study of the responses from a group of patients with toxemia and hypertension in pregnancy. Note the marked responses in the patients with nephritic toxemia, as compared with the preeclamptic and eclamptic patients.

In table 1, we present the biometric analysis of the data on the normal nonpregnant and the normal pregnant women used as controls, illustrating the variations and the means of the fluctuations in the systolic blood pressure caused by the standard stimulus. It is interesting to note that when the patients gave a family history of hypertension,

the mean increases were the same, and when the family history was negative, the mean increases again were the same. The differences, however, are significant.

In table 2 is similarly presented the biometric analysis of the data on the toxemic patients, giving the variations and the means for this group. The mean rise for the group with chronic nephritis is double that for the preeclamptic and the eclamptic group. The increase in the

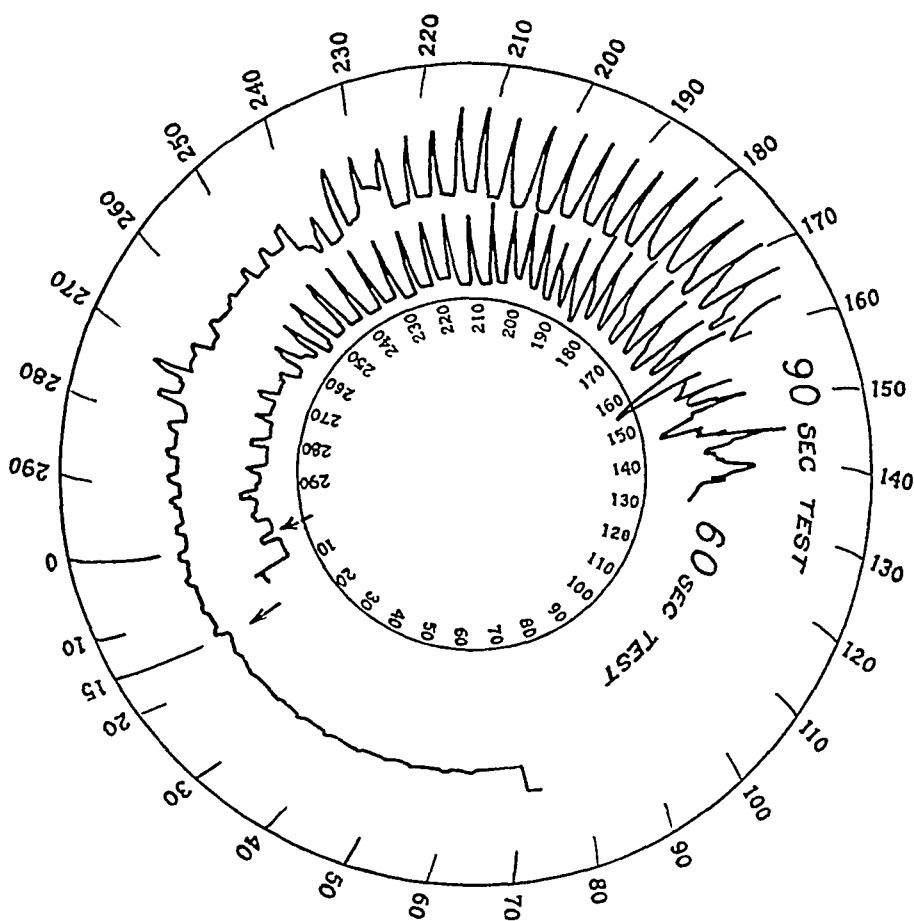


Fig 7—Graph obtained with a Tyco's self-recording sphygmomanometer, illustrating the responses obtained sixty seconds and ninety seconds, respectively, after immersion of the hand in ice-water.

nephritic group is significant. The increase in the preeclamptic and the eclamptic patients is also significant if compared with the data for the pregnant patients who gave no history of hypertension.

#### MECHANISM OF RESPONSE

It appears that the response is purely that of a pain reflex, as suggested by Hines and Brown. The promptness of the reaction excludes

chemical or hormonal factors. If a tourniquet is applied to the arm that is immersed in ice-water and blood pressure readings are taken on the opposite arm, there is no significant variation in the response. The pain reflex is best illustrated when the test is made during labor. The response obtained with ice-water between labor pains is equivalent to the systolic rise recorded during the pains without the application of the ice-water. Furthermore, the response during anesthesia is inhibited.

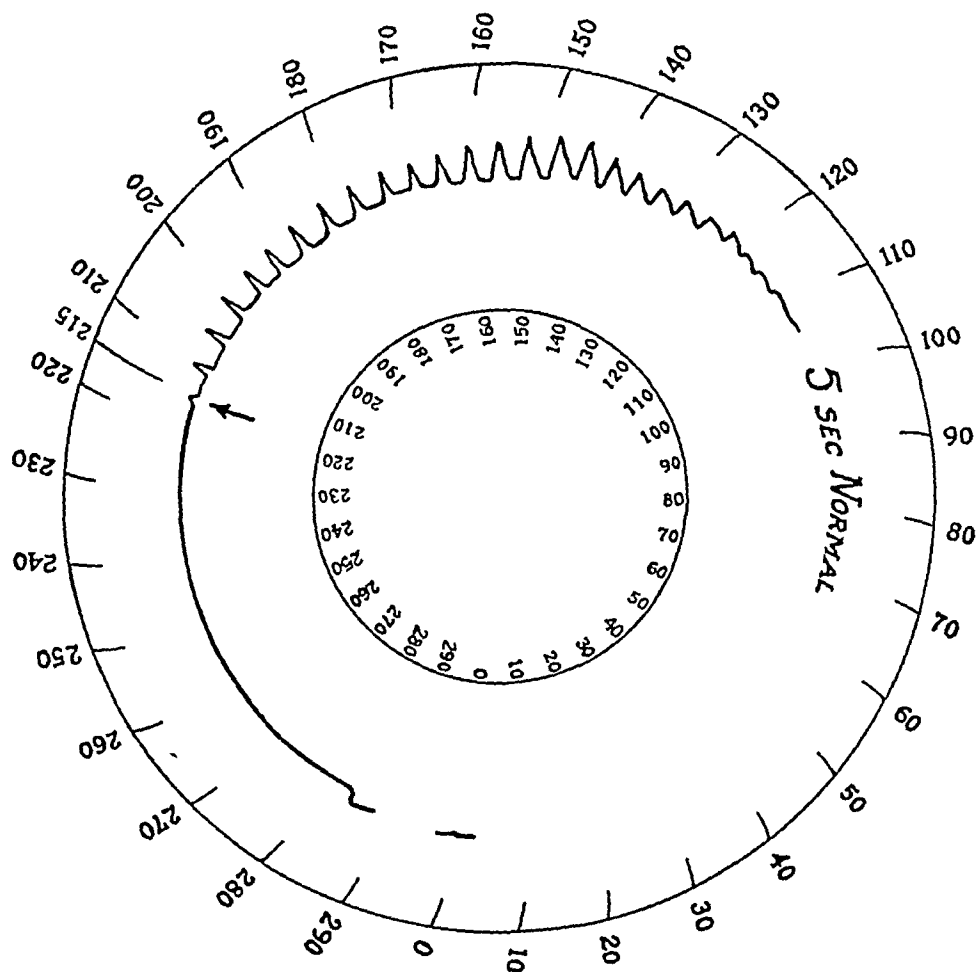


Fig 8—Graph obtained with a Tycos self-recording sphygmomanometer, illustrating the rapid return to normal five seconds after the hand was removed from the ice-water.

#### COMMENT

It is interesting to note that the patients with chronic nephritis exhibited marked vasomotor lability. Five of the patients in this group manifested severe reactions during the test or shortly afterward. The reactions of these five patients were as follows:

The first patient in this group had blurred vision and developed convulsions one hour after the completion of the test.



The second patient complained of intolerable epigastric pain immediately after the test, and within one hour had hematuria and casts in the urine, followed by anuria and collapse of the vasomotor type

The third patient collapsed during the height of the test

The fourth patient had severe epigastric pain, blindness, nausea and emesis during the test

The fifth patient had an increase in blood pressure of 60 mm during the test, and the blood pressure remained elevated for seven days, until she was discharged

The close association of these responses with the test strongly suggests that a vascular disturbance was the cause

A careful analysis was made in this group to determine whether or not there was a correlation between the marked vasomotor response and the renal impairment. The diagnosis of chronic nephritis, as previously stated, was established chiefly from a clinical point of view, with the following criteria in mind: (1) elderly multiparas, (2) a history of previous toxemia of pregnancy, (3) symptoms and findings appearing in the first or second trimester, (4) a history of scarlet fever during childhood with prolonged convalescence, (5) findings of hypertension, albuminuria or edema, and (6) symptoms of headaches, dizziness, nausea, emesis or blurred vision.

Comprehensive laboratory analyses were made in these cases, particular attention being given to the nonprotein nitrogen, blood urea nitrogen, urea clearance, output of urine per hour, specific gravity and sediment. The results indicated that all of these patients had a hypertension at that time or had had it at some previous period, and that there was either slight or marked evidence of a renal pathologic process in all of them. However, only a few could be classified as having chronic glomerulonephritis.

Presumably, then, the clinical phenomena which these patients manifested were attributable to alterations in the vascular system. Whether these alterations were initiated by toxic, neurogenic, chemical or hormonal influences was not clear, but they did appear to be characterized by a marked vasomotor lability which strongly identifies the mechanism as being a vasospasm.

If it is assumed that a general arteriolar spasm does occur, there is a possible explanation for the urinary findings: hypertension, edema and eclamptic convulsions.

The influence of vasospasm and vasodilatation on urinary output has been emphasized by many of the early investigators. Bernard<sup>10</sup>

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<sup>10</sup> Bernard, C. *Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme*, Paris, J. B. Baillière, 1859.

and Eckhard<sup>11</sup> sectioned the spinal cord in the cervical portion in rabbits and in dogs. The vascular tension was reduced to 40 mm and urination ceased. Stimulation of the brain stem and spinal cord caused renal vasoconstriction with diminished renal circulation. Ustimovitsch<sup>12</sup> sectioned the renal nerves in dogs, producing vasodilatation and an increased urinary flow. Thus, there is a definite relationship between vascular tension and urinary output.

Intense spasm in the renal vessels may lead to oliguria and even to anuria and, if unduly prolonged, to destruction of the glomeruli and the tubules. This renal anemia may account for alterations in capillary permeability with the consequent appearance of blood proteins (albumin) in the urine. With the precipitation of albuminous material in the tubules, casts may be formed. It is also possible that the occurrence of edema and convulsions is closely associated with the vascular alterations. It is important to note that this group of patients continued to show marked vasomotor lability for months after delivery. At repeated late postpartum visits one could observe the persistence of hypertension in over 50 per cent of these patients.

The relatively small increases in systolic pressure in the eclamptic and preeclamptic groups afford an opportunity for speculation and conjecture. Apparently in these patients the vascular spasm is at its maximum or there is a diminished response to pain stimuli. This has been demonstrated by Spiegler and Schol,<sup>13</sup> who found that eclamptic patients required a greater cathodal closing current to elicit a contraction than did normal pregnant women. Evidently in chronic nephritis the vascular system is more labile and the nervous system more irritable, or there may be some loss of elasticity of the walls of the vessels, which results in a greater response to stimuli.

The number of observations is too small and the period over which the patients have been followed is too short to permit the drawing of any definite conclusions, but the following statements seem justifiable.

A larger series of patients and a more accurate method for determining vascular lability may demonstrate conclusively that the toxemia of pregnancy is closely associated with vascular spasm.

The test may be of value in determining permanent renal vascular damage after delivery.

The test may enable one to detect early in pregnancy those patients in whom toxemia is likely to develop.

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11 Eckhard. Beitr. z. Anat. u. Physiol. **4** 155, 1869.

12 Ustimovitsch. Ber. u. d. Verhandl. d. k. sächs. Gesellsch. d. Wissensch. z. Leipzig, Math.-phys. Cl. **22** 430, 1870.

13 Spiegler, R., and Schol, W. Die galvanische Nerven-Muskelerregbarkeit in der Schwangerschaft und bei Toxikosen, Arch. f. Gynak. **141** 651, 1930.

The test may also enable one to determine early in pregnancy whether or not a patient with a history of previous toxemia is likely to have a recurrence

#### SUMMARY

One hundred and ninety patients were subjected to a standard ice-water stimulus, and blood pressure readings were obtained at definite intervals during the test

Nonpregnant subjects with a family history of hypertension gave more marked responses to the test than nonpregnant subjects without such a family history. Similar results were obtained in a group of pregnant subjects

In a group of patients with toxemia of pregnancy no uniform results were noted during the preeclamptic period or during the eclampsia

Those patients in whose cases a diagnosis of chronic nephritis had been made gave marked responses before, as well as after, delivery. Subsequent laboratory analyses indicated that all of these patients had hypertension at that time or had had it at an earlier period and that there was either slight or marked evidence of a renal pathologic process in many of them. Only a few, however, could be classified as having chronic glomerulonephritis

In five patients belonging to the chronic nephritic group untoward reactions were obtained that identified the condition as a vascular disturbance

Vascular tension as an important factor in the toxemias of pregnancy is emphasized and discussed

The possibilities of the test as an aid in the diagnosis and prognosis of vascular disturbances during pregnancy are considered

# ESTROGENIC, LUTEAL AND GONADOTROPIC HORMONES IN HEMOPHILIA

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In another communication<sup>1</sup> observations were reported on seven patients with hemophilia in whom no demonstrable improvement in the coagulation of the blood or in the clinical state resulted from the oral and parenteral administration of various ovarian and estrogenic substances

The failure to enhance the coagulability of the blood in hemophilia by the administration of an estrogenic substance has been noted by Blaylock,<sup>2</sup> who observed a slight increase in the coagulation time of the blood of his patient with hemophilia one week after starting daily subcutaneous injections of an "ovarian preparation obtained from the fetal fluid of cattle" Brown and Albright<sup>3</sup> similarly observed no beneficial effect in one patient with hemophilia who was given injections of large amounts of estrogenic substance over a period of three days More recently, Brem and Leopold<sup>4</sup> have reported negative observations on the coagulation time and clinical state of a patient with hemophilia given intramuscular injections of extract of whole ovary daily for three weeks, followed by the daily intramuscular injection of estrogenic substance for two weeks

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1 Stetson, R P , Forkner, C E , Chew, W B , and Rich, M L The Negative Effect of Prolonged Administration of Ovarian Substance in Hemophilia, J A M A **102** 1122 (April 7) 1934

2 Blaylock, A Amputation of Arm of Patient with Hemophilia, J A M A **99** 1777 (Nov 19) 1932

3 Brown, R L , and Albright, F Estrin Therapy in a Case of Hemophilia, New England J M **209** 630 (Sept 28) 1933

4 Brem, J , and Leopold, J S Ovarian Therapy Relationship of the Female Sex Hormone to Hemophilia, J A M A **102** 200 (Jan 23) 1934

These results are at variance with those of Birch<sup>5</sup> and others,<sup>6</sup> who have reported a marked diminution in the coagulation time and an improvement in the clinical condition of patients with hemophilia under treatment with ovarian substances and various preparations of so-called "female sex hormones"

The work of Hynek,<sup>7</sup> in 1923, suggested that a substance contained in the corpus luteum might influence the coagulation time of the blood of persons with hemophilia. He reported the normal clotting of blood of patients with hemophilia following the injection of a preparation of corpus luteum. Birch<sup>5b</sup> stated that she had obtained good results from the administration of lutein preparations. However, Neihans,<sup>8</sup> in 1930, observed an improvement in one patient with hemophilia following the transplantation of an ovary devoid of corpus luteum, whereas the transplantation of an ovary containing corpus luteum into another patient with hemophilia resulted in no improvement.

The limitation of hemophilic manifestations to the male sex provides speculative interest in the theory that some substance peculiar to female physiology inhibits the appearance of these manifestations in the female, through whom the condition is transmitted. This theory was strengthened materially by Birch,<sup>9</sup> who failed to detect estrogenic substance in the urine of seven males with hemophilia or in two "transmitters," while extracts from the urine of normal males consistently induced estrus in rats. Brown and Albright,<sup>3</sup> on the contrary, found more than 40 rat units of this substance in a twenty-four hour specimen of urine of their patient with hemophilia before treatment, while there were more than 480 rat units in a twenty-four hour specimen of his urine after the intensive administration of estrogenic substance. No determinations of the estrogenic factor of the blood were reported in this case, but it seems reasonable to agree with the conclusions of these investigators that "the presence of estrin [estrogenic substance] in the

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5 Birch, C. L. (a) Hemophilia, *Proc Soc Exper Biol & Med* **28** 752 (April) 1931, (b) Hemophilia, *J A M A* **99** 1566 (Nov 5) 1932

6 Foord, A. G., and Dysart, B. R. Treatment of Hemophilia by an Ovarian Extract by Birch's Method, *J A M A* **98** 1444 (April 23) 1932. Kimm, H. T., and Van Allen, C. M. Hemophilia: Prevention and Treatment of Bleeding with Ovarian Extract, *J A M A* **99** 991 (Sept 17) 1932. White, C. E. Treatment of Hemophilia with Theelin, *J Oklahoma M A* **25** 304 (July) 1932. Hirst, J. C. The Influence of Female Sex Hormones upon Blood Coagulation of the Newborn, *Am J Obst & Gynec* **26** 217 (Aug) 1933. Spoto, J. S. Treatment of Hemophilia with Ovarian Extract, *J Florida M A* **20** 9 (July) 1933.

7 Hynek, K. Nouvelles considerations sur l'hémophilie, *Ann de med* **14** 122 (Aug) 1923.

8 Neihans, P. Treatment of Hemophilia, *Schweiz med Wchnschr* **60** 18 (Jan 4) 1930.

9 Birch, C. L. Hemophilia and the Female Sex Hormone, *J A M A* **97** 244 (July 25) 1931.

blood stream, presumably in amounts far greater than found in normal women as judged by the urinary excretions did not in itself alter the coagulation time in a case of hemophilia." Brem and Leopold<sup>4</sup> were unable to demonstrate estrogenic substance in the urine of normal males, and in the urine of two patients with hemophilia who had not received treatment or in the urine of one patient with hemophilia during treatment with intramuscular injections of ovarian extract or of ovarian follicular hormone. The difference in technic employed by the various investigators and the little understood nature of the substances tested help to explain the conflicting results obtained.

It is beyond the scope of this paper to present in detail the facts and theories about the various factors designated as "female sex hormones." It is pertinent, however, to describe briefly the differential features of these hormones so far as they concern our problem.

The estrus-inducing substance of the ovary is produced by the graafian follicle, the corpus luteum and the placenta. Its effect is exerted primarily on the lower genital organs of the female, producing growth and vascularization of the uterus and growth and cornification of the vaginal epithelium in animals. It also promotes the development of secondary sex characters, but its administration is without effect on the ovaries except when given in large doses, when it may depress follicular growth, apparently through an inhibitory action on the anterior lobe of the hypophysis. The usually employed measure of potency of estrus-inducing substances is the rat unit of Allen and Doisy, which is equivalent to 5 mouse units.

In normal women who menstruate regularly, the quantity of estrogenic principle in the blood gradually increases during the intermenstrual period to a maximum concentration during the second half of the cycle. Just before and with menstruation the concentration of estrogenic substance in the blood falls rapidly, but if pregnancy occurs the concentration rises slightly during the first three or four months and then rises to a high level by the time of parturition. Urine from pregnant women and amniotic fluid provide two abundant sources of estrogenic substance for commercial use.

An estrogenic hormone is recoverable from the urine and blood of normal males which has a physical and biologic similarity to that found in the female. From a consideration of the available evidence, Mazer and Goldstein<sup>10</sup> concluded that the estrogenic factor found in the male and that found in the female "produce similar reactions in the lower genital tract of the female castrated rodent, that the male sex

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10 Mazer, C., and Goldstein, L. *Clinical Endocrinology of the Female*, Philadelphia, W. B. Saunders Company, 1933.

hormone prevents the appearance of castration atrophy in the seminal vesicles and prostate, that the action of estrin upon the accessory organs of the male animal is still debatable"

The corpus luteum produces, in addition to the estrogenic substance, the lutein hormone, progesterin, the demonstrated actions of which in adult female animals are to sensitize the endometrium and prepare it for the implantation of the fertilized ovum after the estrogenic factor has exerted its vascularizing effect, to promote the excretion of estrogenic substance and to inhibit ovulation and estrus. It also has an inhibitory effect on uterine contractions. Progesterin is relatively unstable and is not available for ordinary therapeutic use in any considerable amount. Its potency is expressed in rabbit units. As yet, this hormone has not been recovered from the blood or the urine.

The third sex hormone with which we are concerned is one the effects of which have been identified in part with those of the gonad-stimulating hormones of the anterior lobe of the pituitary gland, the anterior pituitary-like gonadotropic hormone. This hormone is non-specific for sex, but in the female two distinct actions have been demonstrated. The action on the ovaries of test animals may be to stimulate the maturation of follicles and hence the production of estrogenic substance (the so-called prolan A, or rho I effect) or to precipitate hemorrhages into the follicles and cause a rapid formation of corpus luteum with its consequent production of progesterin (the so-called prolan B, rho II, or the luteinizing effect). It is debatable whether these effects are dependent on the production of two distinct hormones by the anterior lobe of the pituitary gland or whether the influence is quantitative. The first effect can be evoked by the administration of small amounts of anterior pituitary-like gonadotropic hormone, whereas larger amounts serve to produce luteinization. In the male, the anterior pituitary-like gonadotropic hormone stimulates the testes to produce the testis hormone, and possibly has other effects. The gonadotropic preparations are standardized in terms of the rat unit.

Traces of the gonadotropic factor are constantly present in the blood of every adult, although not always in sufficient quantity to be demonstrable by ordinary methods. During pregnancy the amount is greatly increased to a maximum at the fourth or fifth month, after which there occurs a gradual diminution until term. The large quantity of this hormone recovered in the urine of pregnant women provides most of the supply used in commercial preparations. There is considerable evidence that the hormone found in the urine of pregnant women is not hypophyseal, but rather a placental product with gonadotropic activity.

In this communication we are reporting observations on the coagulation time of the blood and on the gonadotropic principle in the blood

and the gonad-stimulating and estrogenic substances in the urine of two patients with hemophilia during control periods when no particular therapy was employed and while receiving the various preparations to be listed in the quantities indicated in charts 1 to 3. Two other patients were observed while receiving no therapy and after one subcutaneous injection of the anterior pituitary-like gonadotropic hormone.

Each of the patients since infancy or early childhood had experienced characteristic episodes of hemophilia, including hemarthroses. One or more members of the family of each was similarly affected. During control periods and when receiving therapy, each of the group occasionally showed mild manifestations of bleeding. In none were there any significant abnormalities of the formed elements of the blood other than a mild degree of hypochromic anemia. All had received large doses of ovarian substance without benefit, as reported previously.<sup>1</sup>

#### MATERIALS

The preparations used in carrying out the tests were

1 Follutein, the anterior pituitary-like gonad-stimulating hormone obtained from the urine of pregnant women, which stimulates the ovaries of rats, mice and rabbits to the maturation of follicles and the luteinization, assayed by the manufacturer to contain 250 rat units per cubic centimeter.

2 Luteo-hormone, a commercial extract of corpus luteum, assayed by the manufacturer to contain 0.04 rabbit unit of "lutein hormone" per cubic centimeter.

3 Luteo-hormon, the same as that described in 3, but assayed to contain 10 rabbit units of "lutein hormone" per cubic centimeter.

4 Theelol, estrogenic substance for oral administration, assayed by the manufacturer to contain 500 rat units per capsule.

5 Theelin, an estrogenic substance for subcutaneous or intramuscular administration, assayed by the manufacturer to contain 50 rat units per cubic centimeter.

In addition, one patient (patient 5) received small doses of roentgen rays over the pituitary region.

The theoretical considerations which prompted the trial of these preparations of hormones should be mentioned. The use of estrogenic substance was based on Birch's<sup>9</sup> observations that there was no estrogenic substance in the urine of hemophilic patients. However, contrary to her observations, the patients reported on here tended to have excessive rather than subnormal amounts of estrogenic substance in the urine. The corpus luteum hormone, progesterin, has been found to enhance the excretion of estrogenic substance in rabbits and in human beings.<sup>11</sup> Assuming that the usually excessive excretion of the estrogenic factor by hemophilic patients signified a high level of this substance

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11 Smith, G. V., and Smith, O. W. Studies on the Urinary Excretion of Estrin, with Especial Reference to the Effect of the Luteinizing Hormone and Progesterin, *Am J Physiol* **98**: 578 (Nov.) 1931.



in their blood stream, it was thought that the administration of preparations of corpus luteum might be beneficial by promoting such excretion.

Excessive menstrual flow in women has often been found to be associated with the appearance of the follicle-stimulating principle in the blood and urine<sup>12</sup>. Since this principle was present in demonstrable amounts in the blood and urine of some of our hemophilic patients and since excessive menstrual flow in women is benefited in many instances by the administration of the gonadotropic hormone found in the urine of pregnant women, it was considered logical to give an anterior pituitary-like gonadotropic hormone a trial.

#### METHODS

The coagulation time of the venous blood was determined by the method of Lee and White, modified as described in a previous communication<sup>1</sup>. Only the time of complete coagulation of the blood is recorded in the present study. For the sake of simplicity, the time of surface coagulation and the coagulation time of the capillary blood measured in a capillary tube, which were determined simultaneously, are not reported. In general they paralleled the complete coagulation time, with perhaps less marked variation.

For the determination of estrogenic substance, a forty-eight hour specimen of urine was collected, acidified with dilute hydrochloric acid and extracted for ten hours with chloroform in a modification of the apparatus for continuous extraction by means of chloroform described by Frank<sup>13</sup>. The extraction of urine of known potency by this method has shown that not all of the estrogenic substance is recovered. A comparison of our figures on the urine of normal males with some of the figures reported in the literature indicates that other methods of extraction may be more efficient (we have experimented subsequently with other methods and have found that, although none of them give a quantitative recovery, the Kurzrok method [that used by Brown and Albright<sup>3</sup>] yields more than other methods so far tried). However, since the urine of both hemophilic and normal males was extracted by the same process, the results reported are comparable.

[NOTE—Since this work was done we have discovered that the boiling of urine with 15 per cent hydrochloric acid often results in as much as a twenty-fold increase in estrogenic potency. A study of the existing methods of extracting the estrogenic substance of urine has revealed that none of them can be counted on to give a complete recovery of the amount actually shown to be present unless the specimens are first boiled with acid. We have also found that the proportion of the "total" estrogenic substance recoverable from untreated specimens is not constant, but depends on unknown and variable urinary factors, so that whatever the extractive agent the results so acquired may not even be considered comparable and are of questionable quantitative significance.—G. V. and O. W. Smith.]

In the early stages of the investigation the residue left after the chloroform had been evaporated was taken up in a physiologic solution of sodium chloride to be tested on spayed female rats. It was found later that with the use of olive oil for this purpose somewhat larger amounts of estrogenic substance were demonstrated.

12 Smith, G. V., and Rock, J. Dysfunctional Uterine Bleeding, *Surg., Gynec. & Obst.* **57** 100 (July) 1933.

13 Frank, R. T. Rôle of the Female Sex Hormone, *J. A. M. A.* **97** 1852 (Dec. 19) 1931.

There were normal controls for both methods (chart 3). Not all the chloroform was distilled off before the addition of the physiologic solution of sodium chloride or olive oil, the last of the evaporation being performed in a small receptacle on the steam bath. The material was injected first into two rats in amounts testing for 4 rat units. If neither rat showed estrous smears (a negative reaction) the material was tested for 2 rat units, which exhausted the material. With specimens of urine containing more than 4 rat units it was possible to use from four to eight rats for the final assay.

In testing for the gonadotropic factor, from 5 to 10 cc of blood serum, or the amount of urine equivalent to 10 mg of creatinine, was extracted by the Aschheim-Zondek method, i. e., the material was shaken with five volumes of a 95 per cent solution of alcohol, was then allowed to stand overnight and was centrifugated. The precipitate was washed with ether and taken up in 6 cc of physiologic solution of sodium chloride for injection into immature female rats. Urine or blood serum from normal males in these amounts has no effect on the ovaries of immature rats. Any grossly apparent enlargement of the ovaries or uterus was considered a positive reaction.

### RESULTS

Patient 1,<sup>14</sup> a 27 year old Jewish man, the brother of the patient in case 6, was completely ambulatory during the course of the observations recorded in chart 1.

Period 1 shows the fluctuation of the coagulation time of his blood during eight months when no specific therapy was given other than one subcutaneous injection of follutein. This period demonstrates the marked fluctuations of the coagulation time which occurs spontaneously in untreated patients with hemophilia and which must be recognized when one attempts to evaluate the effect of therapy. The increased coagulation time during the winter suggests a seasonal variation, which we have observed in other patients with hemophilia.

On the seventh day of period 3 the coagulation time was increased to eight hours and fifteen minutes, and there developed a large hematoma of the shoulder. On the last day of the period the coagulation time had diminished, but the patient had slight bleeding from his gums. No treatment was given during the ensuing twenty-six days (period 4), during which the coagulation time was comparable to that recorded in the latter part of period 1.

Patient 5, a 28 year old man of German extraction, was in the hospital almost continuously for two years. The therapy he received and the observations on the coagulation time of his blood are recorded in chart 2.

During periods 2, 3 and 4 the average coagulation time was longer than that during the preceding control period. On the last day of period 3 a small hematoma developed on the dorsum of one hand without known trauma, and on the tenth day of period 4 he experienced slight bleeding

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14 The numbers correspond to those assigned the patients in our previous report.<sup>1</sup>

around a tooth. The increase in the coagulation time during periods 2, 3 and 4 is striking, but not sufficient to be of itself significant, as it is not beyond the range of spontaneous fluctuation which has been encountered in this patient and in others with hemophilia (chart 1, period 1). Eight months before this series of observations, he had received three subcutaneous injections of 200 rat units each and three injections of 300 rat units each of a different preparation of an anterior pituitary-like gonadotropic hormone ("Antuitrin S") over a seven day period. Before treatment the coagulation time was four hours and five minutes, on the sixth day it had diminished to one hour and ten minutes,

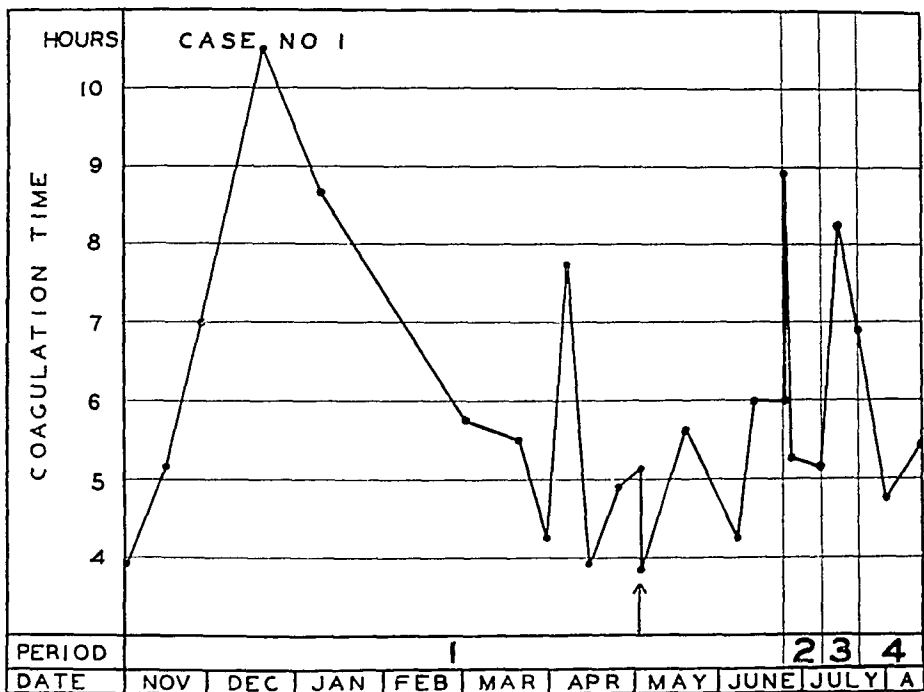


Chart 1 (case 1) —A record of the coagulation time of the venous blood during the indicated periods. In period 1 (eight months) there was no therapy other than one subcutaneous injection of 250 rat units of follutein on May 3 (shown by the arrow). In period 2 (eleven days) a single intramuscular injection of 4 rabbit units of luteo-hormon was given followed by ten daily intramuscular injections of 0.04 rabbit unit of luteo-hormon. In period 3 (fourteen days) 19 rabbit units of luteo-hormon was given in six intramuscular injections. In period 4 (twenty-six days) there was no therapy.

and five days after treatment was discontinued it was two hours and fifteen minutes. The treatment is comparable to that given in period 2, but the behavior of the coagulation time of the blood in the two periods is absolutely contrary.

The three weekly exposures to the roentgen rays given in period 9 were in accord with the technic and dosage described by Mazer and Goldstein,<sup>10</sup> by which they claimed to stimulate the production of the

gonadotropic principle of the anterior pituitary gland in persons with gynecological disturbances (127 kilovolts, 5 milliamperes, filtered with 5 mm of aluminum at a target distance of 14 inches for five minutes over the pituitary region) The increase in the coagulation time following the initial drop after the first treatment might be construed as evidence of a harmful effect of the treatments, which were continued through the subsequent control period It is certain that the treatment failed to enhance the coagulability of the blood

The administration of estrogenic substance (theelin) subcutaneously was carried on during the fifty-one days of periods 11 and 12 The curve recording the coagulation time during these periods shows a marked downward course, covering a range of nearly four hours However, the first determination in control period 13 was made only two days after the last injection of theelin and is at essentially the same level as before treatment

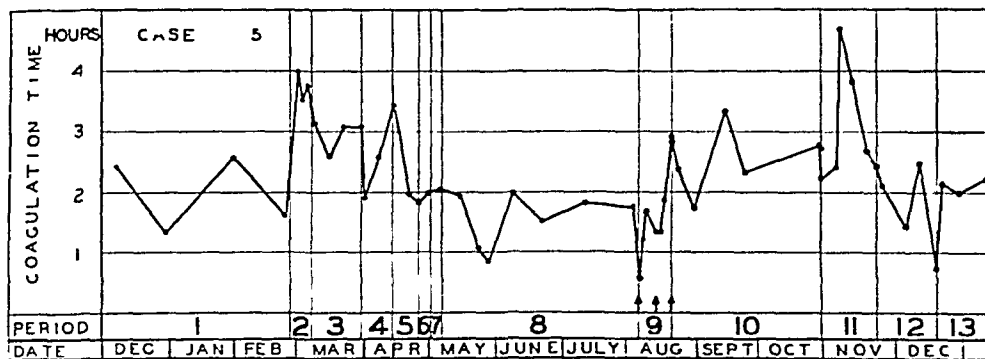


Chart 2 (case 5) —A record of the coagulation time of the venous blood during the indicated periods In period 1 (eighty-five days) there was no therapy In period 2 (nine days) 250 rat units of follutein was given subcutaneously daily In period 3 (twenty days) 125 rat units of follutein was given subcutaneously daily In period 4 (fifteen days) 125 rat units of follutein was given subcutaneously, and 1,500 rat units of theelin was given orally, daily In period 5 (twelve days) 125 rat units of follutein was given subcutaneously, and 0.04 rabbit unit of luteo-hormon was given intramuscularly, daily In period 6 (seven days) 125 rat units of follutein was given subcutaneously, and 0.08 rabbit unit of luteo-hormon was given intramuscularly, daily In period 7 (five days) 250 rat units of follutein was given subcutaneously, and 0.08 rabbit unit of luteo-hormon was given intramuscularly, daily In period 8 (eighty-eight days) there was no therapy In period 9 (fifteen days) there were three roentgen ray exposures over the pituitary region In period 10 (sixty-nine days) there was no therapy In period 11 (twenty-five days) 50 rat units of theelin was given subcutaneously every second day In period 12 (twenty-six days) 50 rat units of theelin was given subcutaneously twice a week In period 13 (thirty days) there was no therapy

Formerly<sup>1</sup> we were unable to demonstrate a change in the coagulation time resulting from the daily subcutaneous injection of 50 rat units of estrogenic substance The injections as carried out in periods 11 and

12 were undertaken because of the statement of Wiedemer<sup>15</sup> that the daily injection of 1 cc of theelin is too frequent for adolescent children, causing the coagulation time to increase, whereas the administration of 1 cc of theelin every second or third day will, in two or three weeks, bring the coagulation time down toward normal, where it can be maintained by two injections a week

Each of two other patients (patients 3 and 6) received one subcutaneous injection of 250 rat units of follutein in order to observe the immediate effect of a single injection of the anterior pituitary-like hormone. Determinations of the coagulation time were made immediately preceding and three hours after the injection. Patient 3 had received 8 Gm of desiccated whole ovary (derived from 48 Gm of the fresh gland) by mouth daily for twelve days without apparent influence on the coagulation time of his blood. Before the injection of follutein his blood coagulation time was four hours and five minutes, three hours later it was five hours and five minutes. Patient 6 had received no treatment for six months. The coagulation time of his blood before the injection of follutein was six hours and forty-five minutes, three hours later it was four hours and thirty-five minutes. Patient 1 (chart 1), in a similar experiment, had a coagulation time of five hours and ten minutes before the injection and of three hours and fifty minutes three hours later. These changes in the coagulation time demonstrate no consistent tendency and indeed are scarcely beyond the limits of technical error. They cannot be interpreted to indicate an immediate effect from the injection of follutein.

*Determinations of the Estrogenic and Gonadotropic Factors in the Blood and Urine*—The first determination of the estrogenic substance in a forty-eight hour specimen of urine from patient 1 (chart 1) was made from Jan 10 to 12, 1933. The specimen contained between 12 and 20 rat units, which was the largest amount recovered from a forty-eight hour specimen of this patient's urine during the control period (period 1). The coagulation time of the blood on the day the collection of urine was started was eight hours and thirty-seven minutes, a long coagulation time, but near the beginning of a period of improved blood clotting. The next largest amount of estrogenic substance recovered was between 8 and 12 rat units in a specimen collected from March 29 to 31. On the following day the coagulation time was four hours and fifteen minutes. One week later, with from 2 to 4 rat units of estrogenic substance in a forty-eight hour specimen, the coagulation time was seven hours and forty-five minutes. In this instance, the increase in estrogenic substance in the urine occurred coincidentally with a

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<sup>15</sup> Wiedemer, quoted by Mills, C A. Hemophilia, J Lab & Clin Med 17 932 (June) 1932

lessened coagulation time immediately preceding an increase, whereas in the former instance the diminishing coagulation time continued to decrease, as did the excretion of the estrogenic substance. Six other determinations of the excretion of estrogenic substances in forty-eight hour specimens showed values varying from less than 2 rat units, on March 20, to more than 8 rat units, on March 3, without relation to the length of the coagulation time.

Two 10 cc specimens of urine from patient 1 tested for gonadotropic effect gave negative results. Of eight 5 cc specimens of blood serum tested, four had a definite follicle-stimulating effect. Follutein (250 rat units) was injected subcutaneously after one positive reaction. The blood serum drawn three hours later gave a weakly positive reaction. In each instance but one, a positive follicle-stimulating effect was associated with a longer blood coagulation time than was observed when the gonadotropic factor was not demonstrated in the blood serum. The one exception was on January 10, when the serum failed to show the gonadotropic factor and the coagulation time was higher than at any of the subsequent determinations in period 1.

During the administration of luteo-hormon, in periods 2 and 3, there was a persistently high excretion of estrogenic substance which was greater than this patient had shown before starting the treatment and which was equaled only by the values obtained in one determination on the urine from a normal male and three scattered determinations on the urine of patient 5 during a control period (chart 2, period 8). These observations are in accord with the work of G V and O W Smith,<sup>11</sup> previously cited. No correlation could be established between the amount of the estrogenic factor excreted and the length of the coagulation time.

A determination of the excretion of the estrogenic substance in a forty-eight hour specimen of urine of patient 5 was made on Sept 9, 1932, three months after he had received "Antuitrin S" for six days. The amount excreted was found to be more than 8 rat units. At the start of period 1 (chart 2), three days after discontinuing the daily administration of 8 Gm of desiccated ovarian substance, the excretion of estrogenic substance in a forty-eight hour specimen was between 12 and 20 rat units. Two days later the blood coagulation time shown by the first test of period 1 was two hours and twenty-five minutes. Thereafter until the end of period 7 the excretion of estrogenic substance fluctuated from less than 2 rat units to between 4 and 8 rat units per forty-eight hour quantity of urine, regardless of the change in the coagulation time of the blood or of the therapy given. Two days after period 7, however, the excretion of estrogenic principle in a forty-eight hour specimen increased to more than 30 rat units, and it remained at a high level, while the coagulation time fell to fifty minutes and subsequently increased.

to two hours, at which approximate level it remained. Determinations of the amount of estrogenic substance excreted were not carried out beyond the end of period 8.

Ten cc of urine from patient 5 (chart 2) was tested for follicle-stimulating effect on eight occasions. Two tests were negative and one positive in period 1, before follutein was administered, and three were negative and two positive during periods 2 and 3 while follutein was being given. One 10 cc sample of this patient's blood serum taken in period 1 produced no follicle-stimulating effect, while one 5 cc sample gave a positive reaction. Seven 5 cc samples of serum were tested for the follicle-stimulating effect in periods 2 to 7, inclusive. Of these, four gave negative, and two, positive reactions, and in one instance the

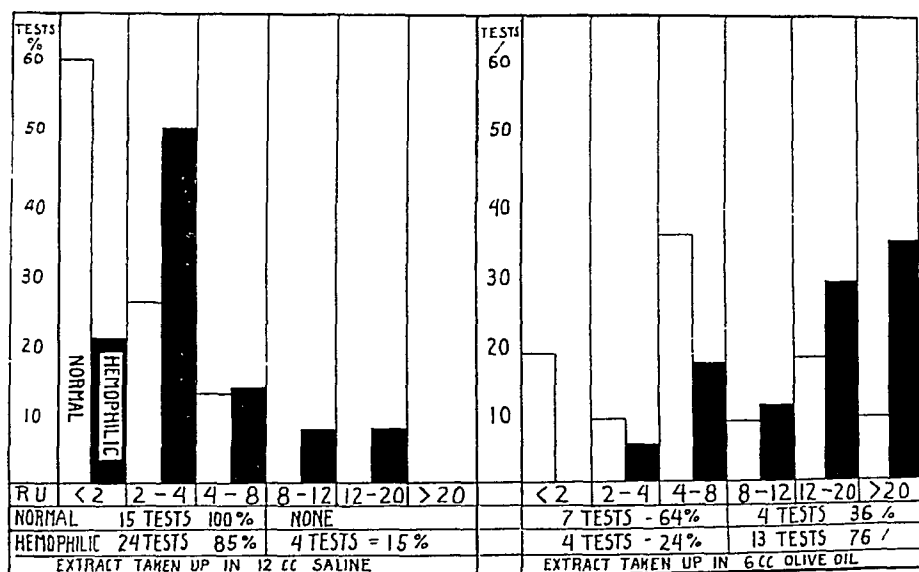


Chart 3—A graph showing the relative amounts of estrogenic substance recovered in forty-eight hour specimens of urine of twenty-six normal males and forty-five persons with hemophilia. The white columns represent the percentage of tests on the urine of normal males yielding the indicated quantity of estrogenic substance expressed in rat units per forty-eight hour specimen of urine. The black columns represent the percentage of tests on the urine of the persons with hemophilia. The number and percentage of the specimens yielding less than 8 rat units per forty-eight hour specimen of urine and those yielding more than 8 rat units are indicated at the bottom of the chart.

effect was doubtful. In general, the positive reactions of the blood were associated with longer coagulation time than were the negative reactions. However, ten days after the end of period 7, a strongly positive reaction was obtained with blood the coagulation time of which was one hour and fifty minutes, an average time for this patient.

*Determination of Estrogenic Substance in the Urine of Hemophiliac and Normal Males.*—The quantity of estrogenic substance contained in

forty-five specimens of urine voided over a forty-eight hour period was determined in six patients with hemophilia. Similar determinations were made on twenty-six specimens from twenty-six normal males of comparable age (chart 3). The specimen of urine from the patients with hemophilia comprising the series were collected only during control periods, while the patients were receiving no specific therapy, and in no instance were specimens included which had been passed less than eight days after therapy was discontinued.

In twenty-eight of the determinations on the urine from patients with hemophilia and in fifteen of the tests on specimens from normal subjects, the fraction of extract for injection into the test animals was taken up in 12 cc of a physiologic solution of sodium chloride. In the tests on seventeen specimens from patients with hemophilia and on eleven specimens from normal males, 6 cc of olive oil was used for this purpose. The yield of estrogenic substance was found to be greater with the latter technic, as is shown in chart 3.

The number of tests is too small to permit dogmatic mathematical analysis, but the recovery from the urine of the patients with hemophilia of an estrus-inducing substance has been demonstrated indisputably. The quantity of estrogenic substance excreted by some normal males, as assayed in forty-eight hour specimens of urine, was greater than that excreted by some patients with hemophilia in a similar period. Considered as a group, however, our patients with hemophilia excreted a greater amount of the substance than did our group of normal males.

#### CONCLUSIONS

As a result of these observations we feel confident that persons with hemophilia have no lack of estrogenic substance in their urine and, although it does not necessarily follow, probably have no deficiency of this principle in their blood. Our observations fail to substantiate the theory that an absence of this hormone is responsible for the impaired coagulability of the blood in persons with hemophilia. Conversely, we have been unable to alter the characteristic fluctuations of the prolonged coagulation time of the blood in hemophilia by the administration of estrogenic substances.

The frequency with which increases in the coagulation time of the blood were associated with a demonstrable amount of the gonadotropic factors in the blood and the somewhat increased blood coagulation time found in patient 5 while he was receiving follutein, an anterior pituitary-like gonadotropic substance, and after exposure of the pituitary region to stimulating doses of roentgen rays are observations which could be construed to indicate that the gonad-stimulating hormone of the anterior pituitary gland may contribute an adverse factor to blood clotting in hemophilia. However, the absence of demonstrable amounts of the



gonadotropic factor in the blood of persons with hemophilia while a prolonged coagulation time was maintained argues against the essential importance of this factor in influencing the coagulation time

We have discovered no evidence to suggest that any of the hormones considered exert any fundamental influence on this sex-linked, hereditary disorder of blood clotting

#### SUMMARY

Two patients with hemophilia have been studied for ten and thirteen months, respectively, while receiving no specific therapy and while receiving preparations of estrogenic substance by mouth and subcutaneously, the hormone of the corpus luteum intramuscularly and the gonad-stimulating hormone from the urine of pregnant women subcutaneously. One patient was exposed to stimulating doses of roentgen rays over the pituitary region

The administration of such hormones to these patients with hemophilia was not associated with a demonstrable improvement in the clinical condition or with a significant diminution in the coagulation time of the blood

Frequent determinations revealed no relationship between the fluctuation of the coagulation time of the blood and the amount of estrogenic substance recovered from forty-eight hour specimens of urine

The urine from untreated patients with hemophilia usually contained a larger amount of estrogenic substance than did the urine from normal males of comparable age

During the administration of the anterior pituitary-like gonadotropic hormone, after roentgen irradiation of the pituitary region and sometimes in association with a demonstrable amount of the gonadotropic factor in the blood, it took longer than usual for the blood to clot

In view of our data we conclude that the hormones investigated in this study do not exert a fundamental influence in hemophilia

# PHYSICAL CONSTITUTION AND DISEASE

## II ABSENCE OF CORRELATION BETWEEN THE ANATOMIC CONSTITUTION AND THE PREDISPOSITION TO DIABETES MELLITUS, CHOLECYSTITIS AND PEPTIC ULCER

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When you can measure what you are speaking about and express it in numbers, you know something about it, but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind —  
*Lord Kelvin*

We shall see that the connection between physical diseases and the external configuration of the body is less close than has been assumed —*Jonathan Hutchinson* *The Pedigree of Disease*, London, 1884

Since the publication of our first paper on this subject<sup>1</sup> an opportunity was taken of reviewing the literature dealing with this subject in greater detail. After a thorough search of the older literature it was surprising to find how little attention had actually been paid to the matter in what could be considered a useful sense. The most plausible reason for this appears to be that for many centuries the subject was confused by the haze of the four humors, and obviously so long as constitution rested on this mythical foundation progress could not be made. What ensues is supplementary to the review given in the previous report and is the result of a search in the writings of about thirty of the better known clinicians from the Greco-Roman period of medicine onward.

The first reference to constitution with the modern meaning, in the Latin, was found in the works of Cicero<sup>2</sup> (106-43 B C). He translated εὐσθένεια, that is, a good state of health, as *firma corporis constitutio*<sup>2</sup>. The word "constitution" in the sense of "the physical nature or character of the body in regard to healthiness, strength, vitality of the body" was used in English as early as 1553<sup>3</sup>.

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1 Feigenbaum, J, and Howat, D. The Relation Between Physical Constitution and the Incidence of Disease, *J Clin Investigation* **13** 122, 1934

2 Cicero. *De officiis*, paragraphs 3, 33 and 117

3 *A New English Dictionary on Historical Principles*, edited by James A H Murray, New York, Oxford University Press, 1893, vol 2

Celsus (53 B C -A D )<sup>4</sup> appears to be the first of the medical writers of note to recognize that physical constitution as such may exist and may be a factor in the etiology of disease. In the following abstract the implication may be drawn that certain physical characteristics determine the predisposition to diseases

"But above all things everyone should know the nature of his constitution because some are slender, others fat, some are hot, others more cold, some are moist, others dry *there are very few who have not some weak part of the body*"<sup>5</sup>

It was only seventeen centuries later that John Huxham (1692-1768) presented the first scientific definition of constitution, including in it the factors of heredity and environment. Huxham considered fever as the struggle of nature to relieve herself of something oppressive, and in discussing the efforts of the body to accomplish this end he maintained that the constitution of the body must be taken into account. Huxham<sup>6</sup> defined constitution as follows

Probably all that we call firmness of body and strength of constitution, is originally owing to the rudimental strength and stamina of our bodies, and on the strong or weak texture of them in a great measure, depends our future prosperous or adverse health. There was indeed a determined constitution and strength of fibres designed by nature, and any deviation from it may be called a disease, which may arise from weakly parents, errors in diet, exercise, and many other things and this deviation I would have heedfully attended to in practice

Of all the medical writers preceding the modern period John Hunter (1728-1793) adopted the most scientific attitude toward the various aspects of constitution. About one hundred and fifty years ago he recognized the problems bound up with the subject. Curiously enough his ideas concerning constitution are not referred to by students of the subject whose work has been consulted. It is therefore worth while to examine Hunter's views in some detail.

Hunter<sup>7</sup> believed that the interaction between the particular constitution of the human body and pathologic influences was responsible for the symptoms and signs of disease. He indicated this in the following roundabout and whimsical manner: "The most simple idea I can form of an animal being capable of disease is, that every animal is endued with a power of action and a susceptibility of impression, which impression forms a disposition, which disposition may produce action,

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4 Celsus, cited by Huxham<sup>6</sup>

5 Celsus, Aurelius Cornelius. On Medicine, London, E. Cox, 1831, vol. 1, p 34

6 Huxham, John. An Essay on Fevers to Which is Now Added a Dissertation on the Malignant Ulcerous Sore-Throat, ed. 4, London, J. Hinton, 1764, p. 27

7 Hunter, John. The Works of John Hunter with Notes, edited by J. F. Palmer, London, Longman, Rees, Orme, Brown, Green and Longman, 1835, vol. 1, p. 34

which action becomes the immediate sign of the disease" It has been recognized by all workers interested in the subject that, whatever may be responsible for the varieties of reaction to disease, these could not easily be altered by artificial means Hunter expressed this opinion in the following excerpt "The susceptibility of the constitution may be increased, so as almost to be similar to a new formation, but is never originally formed by art"<sup>8</sup> "Art" is taken to imply environmental circumstances or treatment With the foregoing two preliminary views Hunter proceeded to emphasize the fact that certain systems in a person may show a greater susceptibility to disease than others "Thus as the liver in some constitutions is more susceptible to secreting bile, which is its natural action, than it is in others, so also it is more susceptible of its peculiar diseases in some constitutions than it is in others"<sup>9</sup> And the following observation would not be out of place in a modern textbook of bacteriology, with the underlying explanation of the phenomenon still absent, however "Two men equally susceptible may be exposed to the cause of an ague one may have the disease, the other not"<sup>10</sup> Moreover, the tendency of certain persons to display mild or violent reactions to disease-producing influences is stated "For example, some constitutions are more susceptible of inflammatory fevers than of any other fevers, others are more susceptible of putrid fevers (e g, typhoid fever), while either one or the other of these constitutions might have some other disease, either violently or mildly, as smallpox, measles, etc"<sup>8</sup> Furthermore, it is important to appreciate that Hunter realized the complex nature of constitution and that he saw the numerous phases of its application to the study of disease

There is a reference in Hunter's work—the first, so far as can be determined—to the effect of the complexion on the incidence of disease "Fair people are also more susceptible of certain diseases than the dark, as of scrofula The irritable inflammation also is more common in the fair than the swarthy"<sup>11</sup>

It is evident that the historical background of constitution, as understood at present, dates back only about a century and a half Moreover, the unquestioned father of the subject is John Hunter, who in his works pointed the way to numerous problems But constitution did not become a problem for serious investigation until about one hundred years later Indeed it is discouraging to find how little progress has been made in this subject since it was first placed on a scientific basis by Hunter

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8 Hunter,<sup>7</sup> p 303

9 Hunter,<sup>7</sup> p 304

10 Hunter,<sup>7</sup> p 306

11 Hunter,<sup>7</sup> p 308

The current opinion in the past century has been that a person's physical build is one of the factors responsible for his predisposition to a particular disease. This view leads to what has been referred to as the physiognomic diagnosis of disease or disease groups. It represents a long-standing clinical tradition and is based in effect on a *post hoc ergo propter hoc* fallacy. Because a patient suffering from diabetes mellitus may have a certain physical configuration this habitus is said to make him more susceptible to the development of the disease. A more common example perhaps is the view long accepted that the flat thorax of a patient with pulmonary tuberculosis has made him more susceptible to phthisis. It is erroneous to draw such a conclusion, because the disease itself may have produced the changes observed in the thorax, and these may be simply *manifestations* of the disease. There is little doubt that many attributes of the body which have been said to render a person displaying them susceptible to a certain disease have actually been produced by the disease.

In bringing about the change of attitude from belief in the humoral to that in the morphologic predisposition Addison and Hutchinson in England, di Giovanni and Pende in Italy, Kretschmer in Germany, Bauer in Vienna and Draper in the United States all played a prominent rôle. Although the study of physical constitution does not represent the solution of the problem, nevertheless it points the direction for further study of the patient along strictly objective lines. Any one who is at all familiar with the long and involved history which attaches to the subject realizes that this changed attitude toward the problem represents a major advance. It is in this respect that the workers just mentioned made their chief contribution to the study of the subject. Draper brought the work to the point at which he believed that many individual diseases had specific diatheses or types which could be recognized by anthropometric methods. It was at this juncture that the present studies of the subject were undertaken.

The greater part of the work reported here has been alluded to in the previous communication<sup>1</sup> in some detail. It is proposed to analyze the results further in this paper, particularly so far as comparing them with the figures obtained by Draper is concerned.

In all, 192 patients were employed for the anthropometric measurements. Seventy-nine patients were diabetic, 67 suffered from peptic ulcer, and 46 from cholecystitis. Ninety-one were males, and 101 were females. The age groups and the racial distribution were sufficiently alike in the three disease entities to be disregarded without fear of interfering with the validity of the results. Thirty-seven measurements were taken, including various diameters of the head, extremities and trunk. In the case of bilateral measurements of the extremities only the diameters on the left side were obtained. In addition, eight indexes were calculated from the data available. These were worked out only in the instances in which a single diameter of a portion of the body by itself would not convey the complete picture. Since in appraising the various measurements obtained males could be

compared only with males and females with females, the groups with each of the three diseases had to be subdivided into the male and female components, so that six major groups were dealt with statistically

The statistical methods employed need not be considered in detail here, but the following brief comment will clarify much of the discussion that is to follow. In the first place, the mean or average was obtained for each pair of the three groups. Then the differences between the diabetic group and that with peptic ulcer, between the group with peptic ulcer and that with cholecystitis, and between the diabetic group and that with cholecystitis were worked out for both males and females. The standard error of the difference was calculated, and the difference obtained was divided by the standard error. When the quotient ( $t$ ) equaled or exceeded 2 the difference was taken to be of some significance. But in order to eliminate all doubt in the final tables the difference in the same direction had to be present in both the males and the females of the groups compared before it was regarded as actually significant.

A summary of the results is given in table 1. A few of the results may be discussed here, so that the remainder of the table may be studied with greater ease. The upper facial diameter, or the interval between the most prominent part of the maxilla on each side, of the female diabetic patients was found to be greater than that of the female patients with peptic ulcer. But this difference was not observed in the males. In contrast the nasion prosthion (the distance between the bridge of the nose and the interval between the incisor teeth) of the male patients with peptic ulcer was longer than that of the male diabetic patients, but this difference failed to appear in the female patients. Likewise the nasion prosthion was greater in the males with peptic ulcer than in those with cholecystitis, but the difference between the females of these groups was insignificant. The first measurement in the table to show a significant difference for both the males and the females of corresponding disease groups is the bigonial diameter, or the distance between both angles of the mandible. This measurement was greater in the diabetic patients than in those with peptic ulcer. It will be observed that the length of the neck in both the male and the female patients with peptic ulcer is greater than in the diabetic groups. Scrutiny of the complete table reveals that there were significant differences between the various measurements and the diameters in 53 cases, or 19 per cent of the total, but that the males and females differed in the same direction in only 9 instances (18 measurements), or 6.6 per cent. The latter figure is a negligible quantity as far as probabilities in statistical work are concerned. It can be stated categorically that the physical constitution of a patient is not a deciding factor in the etiology of peptic ulcer, cholecystitis and diabetes.

It is relevant to introduce here a warning regarding the interpretation of graphic figures in work of this nature. Unfortunately, graphs can be made to support almost any preconceived hypothesis, depending entirely on the opinions of the author. It is not so with the statistical method adopted in the present study.

TABLE 1—*List of Body Measurements in Which Significant Differences Were Obtained\**

Measurement	Sex	Direction of Differences Between Disease Groups
Facial diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Nasion prosthion	M	Value in patients with peptic ulcer greater than in those with diabetes
Nasion prosthion	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Length of ear	F	Value in diabetic patients greater than in those with peptic ulcer
Length of ear	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Horizontal length of mandibular ramus	F	Value in diabetic patients greater than in those with peptic ulcer
Horizontal length of mandibular ramus	F	Value in diabetic patients greater than in those with cholecystitis
Bigonial diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Bigonial diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Bigonial diameter	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Circumference of neck	M	Value in diabetic patients greater than in those with peptic ulcer
Length of neck	M	Value in patients with peptic ulcer greater than in those with diabetes
Length of neck	F	Value in patients with peptic ulcer greater than in those with diabetes
Length of neck	F	Value in patients with cholecystitis greater than in those with diabetes
Thoracic anteroposterior diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic anteroposterior diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Thoracic anteroposterior diameter	F	Value in diabetic patients greater than in those with cholecystitis
Thoracic lateral diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic lateral diameter	F	Value in diabetic patients greater than in those with peptic ulcer
Thoracic lateral diameter	F	Value in patients with cholecystitis greater than in those with peptic ulcer
Biacromial diameter	F	Value in patients with cholecystitis greater than in those with diabetes
Biacromial diameter	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Circumference of chest	M	Value in diabetic patients greater than in those with peptic ulcer
Circumference of chest	F	Value in diabetic patients greater than in those with peptic ulcer
Circumference of chest	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Circumference of chest	F	Value in patients with cholecystitis greater than in those with peptic ulcer
Length of chest	M	Value in diabetic patients greater than in those with cholecystitis
Umbilical xiphoid diameter	M	Value in diabetic patients greater than in those with peptic ulcer
Breadth of nail	M	Value in patients with peptic ulcer greater than in those with diabetes
Breadth of nail	M	Value in patients with cholecystitis greater than in those with diabetes
Breadth of hand	F	Value in diabetic patients greater than in those with cholecystitis
Circumference of leg	M	Value in diabetic patients greater than in those with peptic ulcer
Length of radius	F	Value in diabetic patients greater than in those with cholecystitis
Length of tibia	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Weight	M	Value in diabetic patients greater than in those with peptic ulcer
Weight	M	Value in patients with cholecystitis greater than in those with peptic ulcer
Upper facial index†	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Upper facial index	F	Value in patients with cholecystitis greater than in those with diabetes
Lower facial index‡	M	Value in patients with peptic ulcer greater than in those with diabetes
Lower facial index	M	Value in patients with peptic ulcer greater than in those with cholecystitis

\* A quotient (t) equal to 2 or higher was considered significant

† The upper facial index equals  $\frac{\text{Nasion prosthion}}{\text{Facial diameter}}$

‡ The lower facial index equals  $\frac{\text{Nasion submenton}}{\text{Bigonial diameter}}$

TABLE 1—List of Body Measurements in Which Significant Differences were Obtained\*—Continued

Measurement	Sex	Direction of Differences Between Disease Groups
Index of neck	M	Value in patients with peptic ulcer greater than in those with diabetes
Index of neck	F	Value in patients with peptic ulcer greater than in those with diabetes
Index of neck	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Index of neck	F	Value in patients with cholecystitis greater than in those with diabetes
Thoracic index I §	M	Value in diabetic patients greater than in those with peptic ulcer
Thoracic index I	F	Value in diabetic patients greater than in those with cholecystitis
Thoracic index II	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Thoracic index II	F	Value in patients with peptic ulcer greater than in those with diabetes
Thoracic index II	F	Value in patients with peptic ulcer greater than in those with cholecystitis
Umbilical index	M	Value in patients with peptic ulcer greater than in those with diabetes
Arm leg index	M	Value in patients with peptic ulcer greater than in those with cholecystitis
Arm leg index	M	Value in diabetic patients greater than in those with cholecystitis
Ponderal index	M	Value in diabetic patients greater than in those with peptic ulcer

§ The thoracic index I equals  $\frac{\text{Thoracic anteroposterior diameter}}{\text{Thoracic length}}$

|| The thoracic index II equals  $\frac{\text{Thoracic length}}{\text{Thoracic circumference}}$

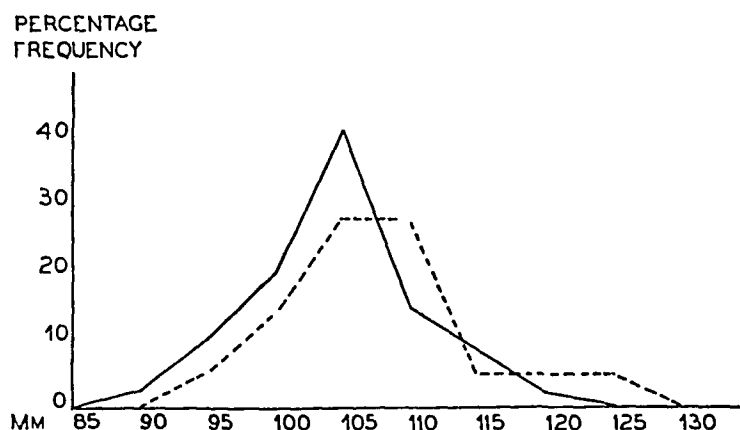


Chart 1—Curves for the bigonial diameter in male patients. The solid line represents the figures for a group of 55 patients with peptic ulcer, the dash line, those for a group of 27 patients with diabetes. The interesting features of these curves are the flattened top of the curve for the diabetic group and the long span of the descending limb. As in the data shown in other charts,  $t$  was significant.

We have included four charts to illustrate the difficulty referred to. In each instance,  $t$  was found to exceed 2, nevertheless no one criterion can be chosen to interpret the figures. This is especially applicable in cases in which the differences are on the borderline of significance. Therefore, this fact must be borne in mind in all work on physical constitution in which statistical analysis plays a part, and the graphic figures alone cannot be accepted.



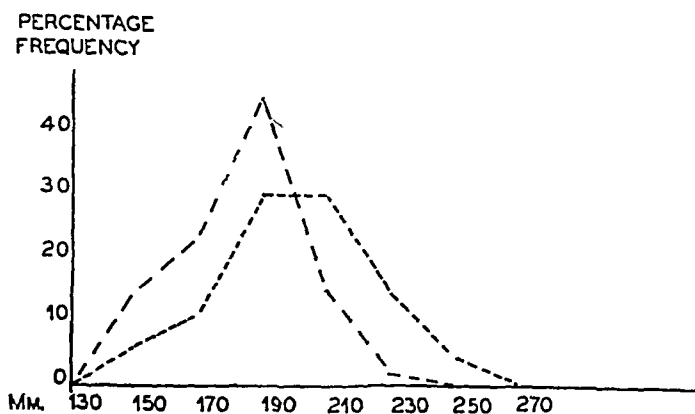


Chart 2—Curves for the thoracic anteroposterior diameter in female patients. The dot-and-dash line represents the figures for a group of 52 patients with diabetes, the dash line, those for a group of 37 patients with cholecystitis. Note again the flat top of the curve for the group with cholecystitis. This type of curve is uncommon in biometric statistics.

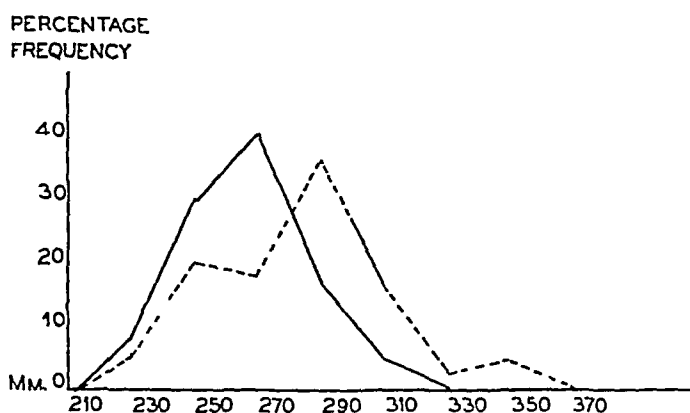


Chart 3—Curves for the thoracic lateral diameter in male patients. The solid line represents the figures for a group of 55 patients with peptic ulcer, the dash line, those for a group of 27 patients with diabetes. The noteworthy features in this chart are the three peaks of the curve for the diabetic group and the comparatively small area of overlapping apparent, as compared with the curves shown in the other charts.

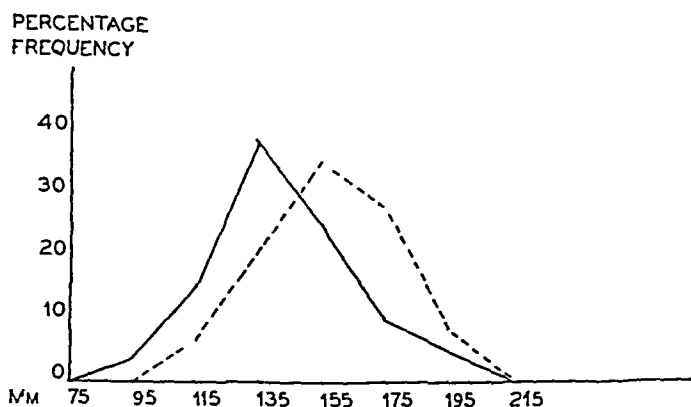


Chart 4—Curves for the umbilical-xyphoid diameter in male patients. The solid line represents the figures for a group of 51 patients with peptic ulcer, the dash line, those for a group of 27 diabetic patients. These curves are the most representative of all those obtained and indicate a sample of the usual graphs for biometric measurements.

From the point of view of a check on the present work it has been especially helpful to turn to Draper's studies on physical constitution incorporated in his first book on this subject<sup>12</sup> Tables with the figures

TABLE 2—*Comparison of Average Measurements for Our and Draper's Series\**

Measurement	Sex	Patients with Peptic Ulcer		Patients with Cholecystitis	
		Our Series	Draper's Series	Our Series	Draper's Series
Cephalic length	M	180	191	179	194
Cephalic length	F	174	182	172	182
Cephalic breadth	M	144	150	145	157
Cephalic breadth	F	139	146	142	149
Length of ear	M	67	65	69	68
Length of ear	F	59	60	61	60
Breadth of ear	M	29	34	28	37
Breadth of ear	F	27	30	27	34
Nasion prosthion	M	70	71	66	70
Nasion prosthion	F	62	68	64	65
Facial diameter	M	110	138	112	142
Facial diameter	F	102	130	105	132
Bigonial diameter	M	105	105	111	105
Bigonial diameter	F	98	97	101	99
Ascending ramus of mandible	M	55	68	58	72
Ascending ramus of mandible	F	49	61	51	67
Horizontal ramus of mandible	M	94	92	98	96
Horizontal ramus of mandible	F	87	91	87	87
Length of neck	M	119	162	108	167
Length of neck	F	101	149	93	143
Circumference of neck	M	338	349	343	391
Circumference of neck	F	317	323	324	342
Thoracic anteroposterior diameter	M	195	206	204	231
Thoracic anteroposterior diameter	F	175	195	184	215
Thoracic lateral diameter	M	266	271	273	294
Thoracic lateral diameter	F	239	195	266	266
Circumference of chest	M	818	875	869	962
Circumference of chest	F	759	825	818	883
Length of chest	M	181	316	190	320
Length of chest	F	164	294	164	288
Biacromial diameter	M	380	377	375	387
Biacromial diameter	F	352	337	339	344
Length of arm	M	748	739	753	884
Length of arm	F	678	651	663	665
Length of humerus	M	301	312	308	312
Length of humerus	F	281	266	277	272
Length of radius	M	262	245	255	249
Length of radius	F	233	217	225	205
Umbilical navel diameter	M	142	209	148	219
Umbilical navel diameter	F	155	201	158	215
Distance from umbilicus to pubis	M	145	160	140	145
Distance from umbilicus to pubis	F	150	150	150	155
Biliac diameter	M	233	285	234	299
Biliac diameter	F	234	286	236	293
Length of lower extremity	M	877	903	898	913
Length of lower extremity	F	813	818	785	822
Length of femur	M	406	467	416	464
Length of femur	F	388	424	370	422
Length of tibia	M	398	363	405	379
Length of tibia	F	379	329	372	334
Height of foot	M	72	73	76	71
Height of foot	F	55	65	65	67
Weight	M	58	59	66	77
Weight	F	57	55	62	72

\* The measurements are given in millimeters

of measurements corresponding to those taken in this work are given in his study Table 2 is a comparison of the figures obtained by Draper and by us

12 Draper, G Human Constitution A Consideration of Its Relationship to Disease, Philadelphia, W B Saunders Company 1924

As for table 1, it is advisable to analyze certain features in this list with a view to facilitating the analysis of the whole table by the individual reader. The first difference of any importance occurs in the facial diameter. One notes that the average for Draper's figures is 28 mm greater for the male patients with peptic ulcer and 30 mm greater for the males with cholecystitis. Similarly for the female group Draper's figures show an increase of 28 mm for the patients with peptic ulcer and of 27 mm for those with cholecystitis. It is important to note, however, that though there are differences between the two sets of figures these differences are small. The explanation of the discrepancy observed is undoubtedly that the surface markings and the technic employed by the investigators differed in some respects. In considering the length of the neck even larger differences are observed, but the same factor can account for them. It is more difficult to explain the difference occurring in the thoracic anteroposterior diameter. In this case Draper's male patients with cholecystitis showed a diameter 27 mm greater than ours, while the female patients with cholecystitis showed an increase of 31 mm. The patients with peptic ulcer did not show this difference. The next striking discrepancy is to be found in the length of the chest. Obviously the landmarks in that measurement must have been different. The arm length of the male patients with cholecystitis was fully 131 mm greater in Draper's than in the present series, but no such divergence is present in any of the three other comparisons in arm length. The variations in the umbilical-xiphoid diameter can be explained by the fact that the points selected by Draper and by us probably differed. The same applies no doubt to the bi-iliac diameter and to the femoral and tibial lengths. With these facts in mind it is apparent that on the whole the two sets of figures are comparable. And it is reasonable to suppose that, had Draper's figures received the statistical treatment accorded the figures of the present work, he would have reached the same conclusion.

Some interesting contributions have been added recently to the current literature on constitution. The following are perhaps the most representative of the point of view expressed in this report. Millard Smith,<sup>14</sup> in a comprehensive study of 102 cases of atrophic arthritis, was unable to find any particular type as characteristic of the disease. A rough classification of habitus showed that his patients fell into the following groups: asthenic, 49, intermediate, 29, sthenic, 24. Moreover the complexion of the whole group was not at all distinctive. Hess and Blackberg,<sup>15</sup> in work which involved the production of rickets in puppies,

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13 This footnote was deleted by the author.

14 Smith, Millard. A Study of One Hundred and Two Cases of Atrophic Arthritis, *New England J Med* **206** 103, 1932.

15 Hess, A. F., and Blackberg, S. N. Constitutional Factors in the Etiology of Rickets, *Am J Physiol* **102** 8, 1932.

concluded that the element of constitution, although important in etiology, did not reside in the physical type of the animal

Some very important as well as thorough and careful work was published recently by Matthew Young<sup>16</sup> from the Institute of Anatomy at University College, London. He studied the physical type of a large number of children with asthma and rheumatism (rheumatic fever?), using a third group of normal children as a control. There were 1,212 children in all. Their ages varied between 6 and 12 years, and from a comparison of the average measurements the children were divided into three two-year groups. Thirty measurements as well as notes regarding the complexion and posture were obtained for each child. The averages, frequency, distributions and variabilities were worked out for the three groups. The conclusion he arrived at is well worth quoting:

The differences in the three groups of children, the asthmatic, the rheumatic and the normal, in respect of the aggregate of physical characters brought under review are relatively so slight that they cannot be considered to support the view that asthmatic and rheumatic children really differ on the average from one another or from the general population of children from which they are drawn in bodily conformation or physical type, though they may possibly, indeed probably, differ in other constitutional traits.

In order to make headway in the study of constitution it will be necessary to step from a consideration of physical constitution, which appears irrelevant, to a consideration of other aspects. In the case of bacterial diseases the immunologic factors which determine the reaction between bacteria and the animal body must be investigated, while in the case of degenerative and metabolic diseases the factors which determine the speed of biochemical processes must be studied. At all events, the opinion held until now of the importance of the physical habitus in the production of disease should be changed.

#### SUMMARY AND CONCLUSIONS

A supplementary historical review of the place occupied by constitution in the study of disease is presented. The contributions of Celsus, Huxham and John Hunter are indicated. There is little doubt that Hunter's opinions of constitution were closer to those generally held today than those of any medical writer in history, and in this respect Hunter should be regarded as the "father of constitution."

The conception that the physical constitution of a person is an important factor in the etiology of disease arose from observations of the effects of certain diseases on the body. At no time were these effects controlled in investigating the subject. Thus a clinical impression

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<sup>16</sup> Young, Matthew. A Study of Rheumatic and Asthmatic Children with Special Reference to Physical Type, *J Hyg* 33 435, 1933.

which is erroneous, namely, that the anatomic habitus is one of the causes of disease, was perpetuated

One hundred and ninety-two patients were observed in this work. Of these 91 were males and 101 were females, 79 patients were diabetic, 67 had peptic ulcer, and 46 had cholecystitis, thirty-seven measurements were taken on each patient, and eight indexes were obtained from the measurements. The diameters and the indexes were all subjected to statistical computations. The results showed that with a few exceptions there were no anatomic characteristics distinctive of patients with diabetes mellitus, peptic ulcer or cholecystitis.

A comparison between the figures obtained by Draper in 1924 and those obtained by us points, on the whole, toward agreement. Opposite conclusions were reached because of the different statistical approach. Young's recently published careful observations on 1,212 children likewise indicate that physical constitution is not related to disease.

Dr W. W. Francis, librarian of the Osler Library, assisted in the search through the older medical literature.

# ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION

REVIEW OF ONE HUNDRED AND SEVEN CLINICAL CASES AND ONE  
HUNDRED AND EIGHT CASES PROVED AT NECROPSY

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The number of clinical, pathologic and experimental observations published on coronary occlusion, its effect and its recognition attest the interest that exists in the subject and its importance as a clinical problem. The very multiplicity of these observations gives rise to the need for their critical evaluation and integration. It is the purpose of this article to make such an integration.

## ANATOMIC CONSIDERATIONS

The first requisite to an understanding of the problem of coronary occlusion is a certain fundamental knowledge of the anatomy of the coronary arteries in the heart of man. The work of Whitten,<sup>1</sup> Gross<sup>2</sup> and Spalteholz<sup>3</sup> on the coronary circulation covers the subject exhaustively. The anterior descending branch of the left coronary artery supplies the anterior portion of the left ventricle and apex and the anterior two thirds of the interventricular septum and gives off a few branches to supply a narrow zone of the anterior portion of the right ventricle. The circumflex branch of the left coronary artery supplies the left third or half of the posterior region of the basal three fifths of the left ventricle. The terminal portion of the right coronary artery, if it has its normal distribution, supplies the posterior third of the interventricular septum and the posterior basal portion of the left ventricle. This distribution of the three main arterial branches establishes three regions of the left ventricle which are the usual sites of myocardial infarction. The anterior apical region and the posterior basal region are the common sites of infarction. In a certain percentage of cases the circumflex

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1 Whitten, M B. The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, *Arch Int Med* 45:383 (March) 1930

2 Gross, Louis. The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, Paul B Hoeber, Inc., 1921

3 Spalteholz, Werner. Die Arterien der Herzwand, Leipzig, S Hirzel, 1924

branch of the left coronary artery supplies the posterior basal portion of the left ventricle and the adjacent interventricular septum as well as its usual zone of ventricular muscle. Occlusion of a vessel having such a distribution will result in infarction in the posterior basal portion of the left ventricle and the adjacent interventricular septum.

#### PATHOLOGY OF MYOCARDIAL INFARCTION

Knowledge of certain facts of pathology is essential to an understanding of the problem of myocardial infarction. A coronary vessel may be occluded suddenly, usually by thrombosis *in situ*, rarely by an embolus. This results in a more or less complete destruction of the tissue in the area that was formerly supplied by the occluded vessel. A mural thrombus frequently forms beneath the myocardial infarction, particularly when the infarction involves the anterior and apical portion of the left ventricle. The presence of an organized thrombus at necropsy beneath a thin fibrous portion of cardiac muscle is strongly presumptive evidence that one is dealing with the healed stage of acute myocardial infarction, in contradistinction to chronic ischemic myofibrosis, which is considered later. Aneurysmal dilatation of the ventricular wall is almost always a sequel of an acute myocardial infarction. Localized pericarditis is observed in 13.8 per cent of cases<sup>4</sup> of acute myocardial infarction, and the presence of chronic pericarditis overlying a region of fibrous replacement in the myocardium is almost certain evidence that the infarction occurred as a result of acute coronary occlusion.

The common cause of chronic fibrosis of the heart muscle is coronary sclerosis. As the degree of this fibrosis is roughly proportional to the degree of narrowing of the main coronary branch supplying the portion affected, it is assumed that the fibrosis results from gradual ischemia. The term "chronic dystrophic fibrosis" is reasonably satisfactory for, and actually suggestive of, such a mechanism. Although gradual narrowing or actual occlusion of the terminal branches of the coronary vessels comes to mind as a possible explanation of scattered fibrous replacement, there are no convincing studies indicating that it is explained by either process, except in a few isolated instances. Localized regions of myocarditis which have healed have to be considered as a cause of localized fibrosis, but the absence of cells characteristic of inflammation in and about these fibrotic regions in cardiac muscle does not support such an assumption. On the other hand, it must be admitted that scattered fibrous replacement occurs in hearts in which the degree of narrowing in the main coronary branches which can be demonstrated anatomically seems hardly sufficient to account for ischemic degeneration. Whether

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<sup>4</sup> Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* 8:245 (Sept.) 1929.

the degree of anatomic narrowing is an accurate index of the degree of functional impairment of the diseased vessel however is an open question

Although this chronic dystrophic fibrosis of the myocardium usually can be distinguished from acute infarction, especially if one bears in mind the criteria of acute infarction just cited there are instances in which such a distinction is impossible. Particularly may this be true if acute infarction is superimposed on chronic infarction.

There is much to make one believe that occasionally coronary thrombosis occurs gradually, the vessel not becoming completely occluded for from one to three days. This may explain some instances of the delayed appearance of electrocardiographic changes indicative of infarction. I have observed a patient with a classic clinical picture of acute coronary occlusion resulting in death after seven hours. At necropsy painstaking dissection revealed marked narrowing of the anterior descending branch of the left coronary artery, but no coronary occlusion was present. There were no changes in the myocardium indicative of acute infarction. Unfortunately, no electrocardiograms were taken in this case. It is an open question whether, had the patient recovered electrocardiographic evidence of coronary occlusion would have been present. This suggests the possibility that in rare instances the absence of electrocardiographic signs of acute infarction following the clinical signs of acute coronary occlusion is an accurate index showing that actual occlusion and acute myocardial infarction did not occur. The only legitimate basis for contending that the electrocardiogram fails to reveal evidence of coronary occlusion rests on cases in which electrocardiographic evidence of acute coronary occlusion is lacking and in which the presence of acute myocardial infarction is proved by necropsy.

Acute myocardial infarction is almost entirely confined to the left ventricle and the interventricular septum.<sup>5</sup> Whitten advanced some anatomic explanations for that fact. Ball and I<sup>5m</sup> showed that infarction of the posterior basal portion of the left ventricle is approximately as common as is infarction of its apex and anterior portion. In the same investigation it was shown that occlusions of the right coronary artery and of the circumflex branch of the left coronary artery were much more frequent than is commonly supposed. We concluded that it is inaccurate to designate the anterior descending branch of the left coronary artery as the artery of coronary occlusion.

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5 (a) Barnes, A. R., and Ball, R. G. The Incidence and Situation of Myocardial Infarction in 1,000 Consecutive Postmortem Examinations, *Am J M Sc* **183** 215 (Feb.) 1932. (b) Parkinson, John, and Bedford, D. E. Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis) *Heart* **14** 195 (Aug.) 1928.



Multiple infarctions of the left ventricle are not infrequently observed, and especially is that true in fatal cases. The presence of multiple infarctions confuses the analysis of the resulting electrocardiographic changes, and in the final interpretation of such cases all possible infarcts must be sought for and their age sequence determined, if possible, by macroscopic and microscopic study.

#### EXPERIMENTAL STUDIES

There have been a great number of studies concerned with the electrocardiographic changes resulting from acute infarction produced experimentally. Gilchrist and Ritchie<sup>6</sup> pointed out that "after injecting silver nitrate into the wall of the left ventricle or interventricular septum,<sup>7</sup> crushing or cutting the apex of the heart,<sup>8</sup> or ligating the coronary arteries and their branches,<sup>9</sup> the electrocardiogram may become transiently monophasic, the R T segment may become deviated from the iso-electric level, or there may be negativity of T which is greatest when the interference with the blood supply of the left ventricle is most pronounced." Furthermore, in axial leads it has been shown that a negative effect on the T wave is produced by cooling the left ventricle,<sup>10</sup> by freezing the right ventricle,<sup>10a</sup> by ligating the

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6 Gilchrist, A. R., and Ritchie, W. T. The Ventricular Complexes in Myocardial Infarction and Fibrosis, *Quart J Med* **23** 273 (April) 1930.

7 (a) Clerc, A. Anomalies électrocardiographiques au cours de l'oblitération coronarienne, *Presse med* **35** 499 (April 20) 1927. (b) Eppinger, H., and Rothberger, C. J. Zur Analyse des Elektrokardiogramms, *Wien klin Wchnschr* **22** 1091 (Aug 5) 1909.

8 Samojloff, A. Weitere Beiträge zur Elektrophysiologie des Herzens. *Arch f d ges Physiol* **135** 417 (Dec 5) 1910.

9 (a) Danielopolu, D. L'angine de poitrine et l'angine abdominale, Paris, Masson & Cie, 1927. (b) Gold, Harry, de Graff, A. C., and Edward D. J. On the R-T Interval in Experimental Coronary Occlusion, *Proc Soc Exper Biol & Med* **23** 664 (May) 1926. (c) Lewis, Thomas. The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* **1** 98, 1909-1910. (d) Otto, H. L. The Extracardial Nerves. An Experimental Study of Coronary Obstruction, *Am Heart J* **4** 64 (Oct) 1928. (e) Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Studies, *Arch Int Med* **22** 8 (July) 1918. (f) Smith, F. M. Further Observations on the T-Wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries, *ibid* **25** 673 (June) 1920.

10 (a) Otto, H. L. The Action of Cold upon the T-Wave of the Electrocardiogram, *J Lab & Clin Med* **14** 718 (May) 1929. (b) Smith, F. M. Some Observations on the Effects of Heat and Cold on the Ventricles and the T Deflection of the Electrocardiogram, *Heart* **10** 391, 1923. (c) Wilson, F. N., and Herrmann, G. R. An Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period of the Heart of the Dog, *ibid* **8** 229 (May) 1921. Eppinger and Rothberger<sup>7b</sup>.

right coronary artery,<sup>11</sup> by bringing about acute right ventricular strain,<sup>12</sup> by stimulating the right accelerator nerve<sup>13</sup> and by injecting alcohol (95 per cent) into the right ventricle<sup>14</sup> A positive effect on the T wave was produced by cooling the right ventricle,<sup>15</sup> by freezing the left ventricle,<sup>10a</sup> by ligating the circumflex branch of the left coronary artery,<sup>11</sup> by effecting acute left ventricular<sup>16</sup> strain, by stimulating the left accelerator nerve<sup>13</sup> and by injecting mercuric chloride or silver nitrate into the right ventricle<sup>7b</sup> A high take-off of the R T component of the electrocardiogram was observed following the injection of mercuric chloride, silver nitrate or alcohol (95 per cent) into the left ventricle,<sup>17</sup> whereas a low origin of the S T component from the S wave occurred when these substances were injected into the right ventricle Otto,<sup>11</sup> using an axial lead, found that ligation of the circumflex branch of the left coronary artery of the dog (this artery supplies the left ventricle exclusively) increased the positivity of the T wave and ligation of the right coronary artery (supplying the right ventricle) caused increased negativity of the T wave, whereas ligation of the anterior descending branch of the left coronary artery (supplying the right and left ventricles about equally) produced effects partially characteristic of each of the first two types of ligation

Smith,<sup>9e</sup> in 1918, studied the effects of ligation of the coronary vessels of the dog on the electrocardiogram He observed remarkable changes in the direction and height of the T wave but did not emphasize significant changes in the level of the R S-T segment He found that ligation of the right coronary artery did not appreciably affect the direction of the T wave Parkinson and Bedford<sup>5b</sup> concluded from this and from their clinical studies that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches that produces characteristic T wave changes" Smith, in his original work did not carry out control experiments in which the pericardium was manipulated, but the coronary arteries were not molested, to determine the effect of pericardial injury on the electrocardiogram

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11 Otto, H L The Effect of Obstruction of Coronary Arteries upon the T-Wave of the Electrocardiogram, *Am Heart J* **4** 346 (Feb) 1929

12 Daly, I De B The Influence of Mechanical Conditions of the Circulation on the Electrocardiogram, *Proc Roy Soc Med* **5** 279, 1923-1924

13 Otto, H L The Extracardial Nerves III Further Observations upon the Relation of the Extracardial Nerves to Heart-Block, *Am Heart J* **4** 59 (Oct) 1928

14 Otto, H L The Ventricular Electrocardiogram An Experimental Study, *Arch Int Med* **43** 335 (March) 1929

15 Eppinger and Rothberger<sup>7b</sup> Otto<sup>10a</sup> Smith<sup>10b</sup> Wilson and Herrmann<sup>10c</sup>

16 Otto, H L The Effect of a Sudden Increase in the Intracardiac Pressure upon the Form of the T-Wave of the Electrocardiogram, *J Lab & Clin Med* **14** 643 (April) 1929 Daly<sup>12</sup>

17 Otto<sup>14</sup> Eppinger and Rothberger<sup>7b</sup>

The work by Whitten and me<sup>18</sup> indicated that occlusion of the right coronary artery producing infarction in the posterior basal portion of the left ventricle caused just as characteristic electrocardiographic changes as did occlusion of the anterior descending branch of the left coronary artery. We pointed out that it was the situation of the infarction and not the vessel which was occluded that determined the type of electrocardiographic pattern obtained.

Mann and I<sup>19</sup> undertook experiments to determine whether experimental occlusion of the right coronary artery of the dog produced deviations of the R S-T segment. In control experiments in which the pericardium was opened but in which the coronary vessels were not disturbed, we obtained all the changes in the T wave described by Smith<sup>20</sup> in his original experiments on ligation, but no significant deviation of the R S-T segment resulted. When the posterior circumflex branch or branches of the left coronary artery or a large branch or branches of the right coronary artery were ligated, marked deviation of the R S-T segment in leads I and III followed in the first forty-eight hours. No attempt was made to explore the various possible sites of infarction in order to determine their correlated electrocardiographic changes. The evidence seemed conclusive that ligation of the right coronary artery produced just as marked changes in the R S-T segment as did ligation of the left coronary artery. The results of these experiments are open to the criticism that it is difficult to exclude the effects of pericardial injury on the R S-T segment and to the further criticism that the areas of ischemia produced by ligation were quite large.

Feil, Katz, Moore and Scott<sup>20</sup> found no change in the R S-T segment of the electrocardiogram after ligating the anterior descending branch of the left coronary artery unless in addition, they clamped the inferior vena cava. They concluded that "R S-T deviation is a manifestation of myocardial ischemia in the production of which coronary occlusion is one factor." They believe that, in addition to coronary occlusion, a reduction in blood pressure was necessary to effect this change in the electrocardiogram. Wood and Wolferth<sup>21</sup> differed with that opinion, and they concluded from their experiments that no additional impairment of the coronary circulation other than that produced

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18 Barnes, A. R., and Whitten, M. B. Study of the R-T Interval in Myocardial Infarction, *Am Heart J* **5** 142 (Dec) 1929.

19 Barnes, A. R., and Mann, F. C. Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *Am Heart J* **7** 477 (April) 1932.

20 Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W. The Electrocardiographic Changes in Myocardial Ischemia, *Am Heart J* **6** 522 (Feb) 1931.

21 Wood, F. C., and Wolferth, C. C. Experimental Coronary Occlusion. Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium, An Electrocardiographic Study, *Arch Int Med* **51** 771 (May) 1933.

by occlusion of a coronary artery was necessary for the production of deviation of the R S-T segment, with which observation Mann's and my experience was in agreement. Wood and Wolfeith further found that the difficulty in obtaining electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery was partially obviated if they did not work with the anterior aspect of the heart exposed, a condition that diminished conduction of the action currents from the heart. More significantly, they found that by means of an anteroposterior thoracic lead, in addition to the conventional leads, it was easy to demonstrate that ligation of the anterior descending branch produced changes in the R S-T segment just as promptly as did ligation of other branches of the coronary vessels.

On the basis of clinical observations it does not appear that a fall in blood pressure is essential to the production of changes in the R S-T segment. These changes frequently are not observed within the first twenty-four hours after coronary occlusion, at a time when the greatest fall in the patient's blood pressure has occurred. Moreover, their classic development a few days later occurs frequently when the blood pressure is rising or has reached the preinfarction level. The picture of cardiac failure, as manifested by edema, dyspnea or cyanosis, is conspicuous by its absence in the average case even for some days after coronary occlusion unless the patient is approaching death. Marked deviations of the R S-T segment frequently develop in cases of mild and nondisabling attacks of coronary occlusion, whereas minimal R S-T deviation alone, sometimes so slight as to make it difficult to recognize the change as evidence of acute infarction, frequently develops when the attack is so grave that death ensues in a few days.

A case reported by Elkin and Phillips<sup>22</sup> seems to have an important bearing on this question. In their first case, a stab wound severed the anterior descending branch of the left coronary artery and the accompanying vein. At the time the first electrocardiogram was taken (forty minutes after the patient was stabbed) the tracing was essentially normal. At this time, because of tamponade of the heart, the radial pulse was imperceptible and the blood pressure could not be determined. After the clot was evacuated from the pericardium, the heart began to beat more strongly and the pulse became perceptible at the wrists. At the end of the operation, the systolic blood pressure in millimeters of mercury was 90 and the diastolic 60. Ten minutes after that, the electrocardiogram began to show a rise of the R T segment in lead I and a depression of the S T segment in lead III. On the second day, the systolic blood pressure was 110, and it ranged between that level and 120 during the patient's stay in the hospital. The electrocardiogram

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<sup>22</sup> Elkin, D. C., and Phillips, H. S. Stab Wound of the Heart. Electrocardiographic Studies of Two Cases, *J. Thoracic Surg.* 1: 113 (Dec.) 1931.

taken thirty-six hours after operation showed classic R T deviations. It seems to me to be a fair assumption that the greatest degree of cardiac failure existed at the time the first tracing was taken. Evidence of some improvement in the function of the heart existed by the time the second tracing was taken, and at that time R T changes began to appear. But thirty-six hours after operation, when the blood pressure was approximately normal, the classic R T deviations were present. Certainly this result of an operation on a human being is not in keeping with the hypothesis that heart failure, in the presence of coronary occlusion, is the essential factor in producing the R T deviation.

The correlation of the site of infarction and the electrocardiographic changes was studied by two additional methods that permitted better localization of the site of infarction than was afforded by the ligation of vessels. Crawford, Roberts, Abramson and Cardwell<sup>23</sup> studied the effect of lesions produced by cautery in various portions of the wall of the two ventricles of the heart of the cat. They found that lesions of the anterior wall of the left ventricle produced tracings of the  $T_1$  type, whereas those in the posterior wall of the left ventricle resulted in tracings of the  $T_3$  type. Lesions produced in the right ventricle resulted in electrocardiograms of the  $T_3$  type, except those located in the anterior basal portion of the right ventricle. After dividing the ventricles of the dog into similar zones and producing lesions in the various portions by the insertion of radon seeds, Haney, Borman and Meek<sup>24</sup> studied the electrocardiographic changes that occurred. They found that lesions of the anterior portion of the left ventricle produced electrocardiographic changes of the  $T_1$  type, whereas lesions of the posterior portion of the left ventricle produced lesions of the  $T_3$  type. The changes observed following injury to the right ventricle were more variable, in general, injury of the anterior portion of this ventricle produced a  $T_1$  type of tracing, and a lesion on its posterior portion produced a  $T_3$  type. These two groups of observers pointed out that, so far as the left ventricle was concerned, their results were in agreement with those of Barnes and Whitten in the localization of infarcts in the heart of man.

Fowler, Rathe and Smith<sup>25</sup> confirmed the observation previously made by Mann and me that injury to the pericardium is followed by successive changes in the T wave of the electrocardiogram. Fowler,

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23 Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, J. C. Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *Am Heart J* 7 627 (June) 1932.

24 Haney, H. F., Borman, M. C., and Meek, W. J. The Relation Between the Position of Experimental Myocardial Lesions in the Dog and the Changes in the RS-T Segment of the Electrocardiogram, *Am J Physiol* 106 64, 1933.

25 Fowler, W. M., Rathe, H. W., and Smith, F. M. The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *Am Heart J* 8 370 (Feb) 1933.

Rathe and Smith pointed out that these changes are associated with demonstrable inflammation of the superficial muscle fibers subjacent to the region of pericarditis. They described the results of ligation of small branches of the coronary arteries, and they observed changes in the T wave that followed. It is not clear how they excluded the influence of pericardial injury on the electrocardiogram in this type of experiment. The electrocardiogram that they obtained (their fig 1) following injury to the pericardium only does not differ materially from that produced by ligation of an anterior branch of the coronary artery (their fig 1). They expressed the opinion that the change in the T wave following coronary occlusion is the primary event and that "the alterations in the R T segment are secondary to the latter manifestations." This conclusion is not in accord with the experience of other investigators. It certainly is not borne out by a study of electrocardiograms of acute myocardial infarction in man. Parkinson and Bedford pointed out that the R S-T segment frequently is displaced before a T wave is present or recognizable, and certainly before it is inverted, an observation which I have frequently confirmed.

Finally, Fowler, Rathe and Smith considered that closure of the smaller branches of the coronary arteries in man is often responsible for the anginal syndrome. They raised the question whether serial electrocardiograms may not be important in detecting these minor injuries to the myocardium. Clinically, I have been impressed with the number of patients suffering from severe coronary disease with marked symptoms of angina pectoris who showed no abnormality of the R S-T segment or of the T wave in the electrocardiogram. This has been true of patients under daily observation, when frequent electrocardiograms have been taken. Wood and his associates<sup>26</sup> observed significant electrocardiographic changes during attacks of angina pectoris, but these changes have been of such a transitory nature that it seems highly improbable that they had their genesis in the occlusion of a small coronary branch.

Although certain discrepancies appear among these observations, there is considerable agreement on the following points. 1 Injury of the pericardium without coronary ligation produces a remarkable series of changes in the form and direction of the T wave. 2 Although the injured region will fail to contribute its normal component to the electric field, the conventional leads may not detect this failure. This is particularly likely to be true of acute myocardial infarction produced by ligation of the anterior descending branch of the left coronary artery.

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26 Wood, F. C., Wolferth, C. C., and Livezey, M. M. Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* **47**: 339 (March) 1931.

3 It is essential in tapping the electric currents of the heart that the heart be surrounded by a suitable conducting medium 4 Acute injury to the right as well as to the left ventricle in animals, whether produced by experimental coronary occlusion or otherwise, results in deviation of the R S-T segment 5 Acute infarction in the anterior portion of the left ventricle in animals produces changes in the R S-T segment that differ characteristically from those that follow infarction of the posterior portion of the same ventricle 6 At least two observations<sup>27</sup> agree that experimental infarction of the anterior portion of the left ventricle produces a  $T_1$  type of electrocardiogram whereas infarction of the posterior portion of the same ventricle produces a  $T_3$  pattern The observers pointed out that their findings were in agreement with the electrocardiographic localization of infarcts in the left ventricle as described in the heart of man<sup>3</sup>

#### CLINICAL ELECTROCARDIOGRAPHIC OBSERVATIONS

Pardee,<sup>28</sup> in 1920, first called attention to the electrocardiogram of acute coronary occlusion He noted that the R S-T levels were disturbed and that the T waves were likely to be tall He pictured the return of the R T level to normal and the sharp inversion in two leads Subsequently,<sup>29</sup> he described the significant electrocardiographic feature of coronary occlusion, whether sudden or gradual, as "the presence in one or more leads, usually in only one, of a downward sharply peaked T wave with an upward convexity of the S-T or R-T interval" (fig 3, C, G)

In 1928, Parkinson and Bedford<sup>30</sup> reported a remarkable series of electrocardiographic tracings obtained following acute myocardial infarction They found that the changes in the RS-T segment of the electrocardiogram fell into two groups, which they designated as  $T_1$  and  $T_3$  types Whitten and I<sup>30</sup> had arrived at a similar conclusion and had accepted their nomenclature The  $T_1$  type of electrocardiogram (fig 1 *A B, C D*, fig 2 *A, B, C, D*) is characterized in its earliest development by a change of the level and contour of the RS-T segment in leads I and II and a depression of the S T interval in lead III The R T interval in leads I and II, but especially in lead I, usually is elevated above the iso-electric line The interval is likely to be convex dome-shaped or sloping downward toward the T wave Diphasic waves

27 Crawford, Roberts, Abramson and Cardwell<sup>23</sup> Haney, Borman and Meek<sup>24</sup>

28 Pardee, H E B An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch Int Med* **26** 244 (Aug) 1920

29 Pardee, H E B Heart Disease and Abnormal Electrocardiograms with Special Reference to the Coronary T-Wave, *Am J M Sc* **169** 270, 1925

30 Barnes, A R Electrocardiographic Localization of Myocardial Infarcts *M Clin North America* **14** 671 (Nov) 1930 Barnes and Whitten<sup>18</sup>

of T waves of a monophasic type are common in the earliest stages. It is important to note that leads I and III act conversely so that the elevation of the R T segment in lead I is opposed by the depression of the S T segment in lead III. The changes in lead II although less in degree, frequently are seen to be similar to those in lead I in cases of infarction in the anterior portion of the left ventricle. At a later stage the monophasic or diphasic type of T wave in lead I, or leads

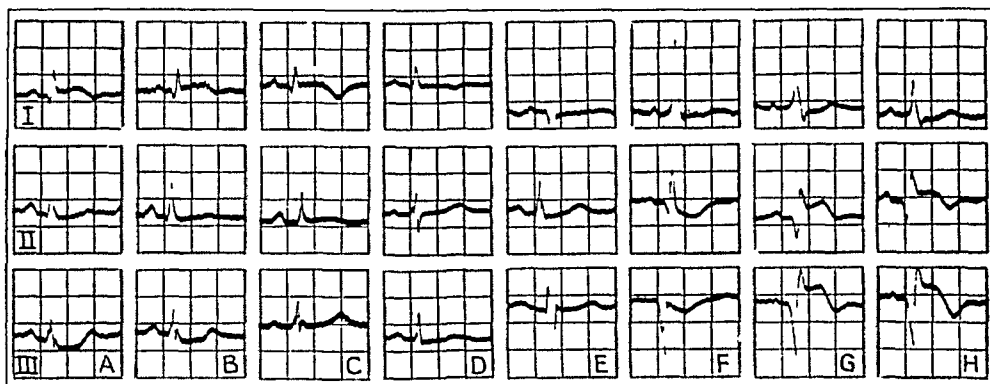


Fig 1—A  $Q_1 T_1$  type of electrocardiogram, taken (A) one day, (B) three days, (C) twelve days and (D) twenty-eight days, after acute coronary occlusion, and a  $Q T_1$  type of electrocardiogram taken (E) two days before, (F) the day of, (G) the day following and (H) three days after, acute coronary occlusion

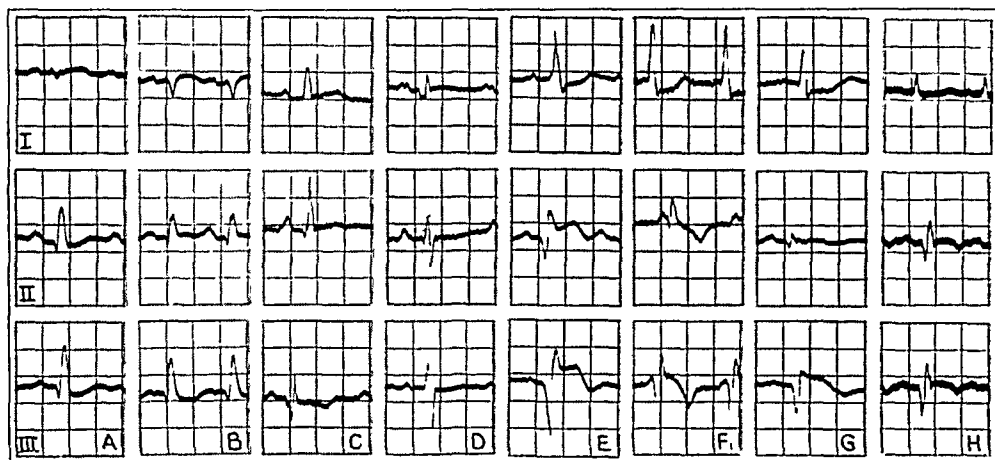


Fig 2—A, B, C and D show a  $T_1$  type of electrocardiogram taken of four different patients during the first week after acute infarction of the anterior and apical portion of the left ventricle. E, F, G and H show a  $T_1$  type of electrocardiogram taken of four different patients during the first week after acute infarction of the posterior basal portion of the left ventricle.

I and II, is replaced by frank inversion. It is worthy of note that as the T wave becomes inverted in lead I, the T wave in lead III remains upright and becomes exaggerated and sharply peaked (fig 1C, fig 3C). Of particular significance in the later stages is the fact that the R T segment arises at or only slightly above the iso-electric level and often



retains the rounded contour in lead I or in leads I and II, preceding the inverted T wave (fig 3 *C,D*) Pitfalls of interpretation will be avoided if one does not interpret RS-T segments in lead I which arise below the iso-electric level as evidence of infarction Conditions producing left ventricular strain are prone to produce a negative T wave in lead I with an S T segment arising below the iso-electric level (fig 5 *A,B,C*) in the absence of myocardial infarction<sup>4</sup>

The  $T_s$  pattern (fig 1 *E,F,G,H*) is characterized by precisely the opposite type of RS-T changes following acute myocardial infarction In its early stages the R T segments are elevated in leads II and III and the S T segment is depressed in lead I (fig 1 *G,H*) A convex, dome-shaped or sloping R T segment preceding the T wave is observed in leads II and III In the later stages the R T segment in leads II and III tends to return to, and eventually reaches, the iso-electric level,

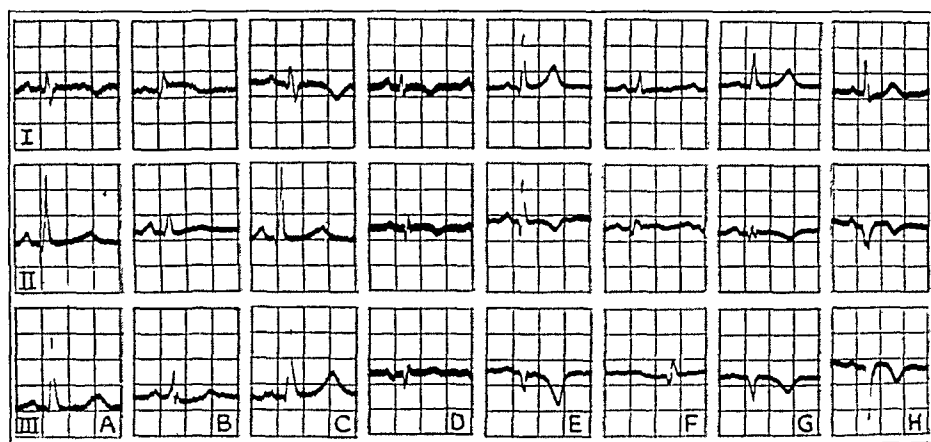


Fig 3—*A, B, C* and *D* show a  $T_1$  type of electrocardiogram taken of four different patients from two to five weeks after acute coronary occlusion *E, F, G* and *H* show a  $T_s$  type of electrocardiogram taken of four different patients from two to five weeks after acute coronary occlusion

and the depressed S T segment in lead I disappears (fig 2*H*, fig 3 *E,G,H*) In this stage inversion of the T wave in leads II and III, with a rounded contour of the RS-T segment, is observed, whereas the T wave in lead I is upright and becomes exaggerated and sharply peaked (fig 3 *E,G*) Here again one must insist in the later stages that the R T segment preceding the negative T waves in leads II and III arises on or above the iso-electric line, if the contours of the segments are to be regarded as evidence of a preceding acute myocardial infarction

It is essential to the recognition of the electrocardiogram of acute myocardial infarction that one be familiar with these typical patterns The feature of these patterns distinguishing them from all other electro-

cardiographic changes is the behavior of the RS-T segment in the first ten days after acute coronary occlusion. It is characterized by a reciprocal relation between the RS-T segments in leads I and III. When the RS-T segment is elevated in lead III (RS-T in lead II is usually simultaneously elevated), the ST segment in lead I is depressed. Conversely, when the RS-T segment is elevated in lead I, the ST segment in lead III is depressed (figs 1 and 2). It has been contended that similar RS-T deviations are encountered in rheumatic fever,<sup>31</sup> in rheumatic carditis following roentgen therapy,<sup>32</sup> in pericardial effusion, under both clinical and experimental conditions,<sup>33</sup> in uremia<sup>34</sup> and in pneumonia.<sup>4</sup> Examination of the tracings submitted in these conditions reveals the fact that they lack the reciprocal relation of the RS-T segments in leads I and III. So far as I have been able to interpret reported tracings, the classic electrocardiogram of acute myocardial infarction is reproduced by no other pathologic process in the heart.

Valuable studies have been reported<sup>35</sup> that stressed the importance of progressive change in the electrocardiogram as evidence of acute coronary occlusion. Although that observation is important and valid, the closer these changes approach the classic electrocardiographic pattern of acute coronary occlusion, the more convincing they become as evidence of an acute closure of a coronary vessel. Progressive changes of the RS-T component are seen in the electrocardiograms of patients with acidosis of diabetes, of patients who have received digitalis, of patients under treatment for myxedema and of certain patients suffering from exophthalmic goiter treated with iodine and by partial resection of the

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31 Cohn, A. E., and Swift, H. F. Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* **39**: 1 (Jan.) 1924. Rothschild, M. A., Sacks, B., and Libman, E. The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *Am. Heart J.* **2**: 356 (April) 1927.

32 Levy, R. L., and Golden, Ross. The Treatment of Rheumatic Carditis by Roentgen Irradiation of the Heart, *Am. Heart J.* **4**: 127 (Dec.) 1928.

33 (a) Katz, L. N., Feil, H. S., and Scott, R. W. The Electrocardiogram in Pericardial Effusion. II. Experimental, *Am. Heart J.* **5**: 77 (Oct.) 1929. (b) Scott, R. W., Feil, H. S., and Katz, L. N. The Electrocardiogram in Pericardial Effusion. I. Clinical, *ibid.* **5**: 68 (Oct.) 1929.

34 Wood, J. E., Jr., and White, P. D. The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, *Am. J. M. Sc.* **169**: 76 (1925).

35 (a) Cooksey, W. B., and Freund, H. A. Serial Electrocardiographic Studies in Coronary Thrombosis, *Am. Heart J.* **6**: 608 (Feb.) 1931. (b) Sigler, L. H. Acute Coronary Occlusion. A Clinical and Electrocardiographic Study of Twenty Cases, *Ann. Int. Med.* **4**: 969 (Feb.) 1931. (c) Wilson, F. N., Barker, P. S., Macleod, A. G., and Klostermeyer, L. L. The Electrocardiogram in Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* **29**: 1006 (May) 1932.

thyroid gland. These changes approximate no predictable pattern and hence are of no value in establishing or excluding the presence of acute coronary occlusion.

Aside from the classic RS-T changes just described, there is no other change in the T wave that indicates with certainty the presence of previous acute coronary occlusion. The T wave of coronary occlusion described by Pardee<sup>29</sup> is highly suggestive of acute coronary occlusion, but it has been closely simulated in cases of at least one other condition. However, whenever typical Pardee T waves are observed in lead I or leads I and II (fig 3 *C,D*), or in the combined leads II and III (fig 3 *E,G,H*), a diagnosis of a previous acute myocardial infarction can never be positively excluded until the heart is examined at necropsy.

Unfortunately, the typical pattern of electrocardiographic changes of acute coronary occlusion frequently is not observed following acute myocardial infarction. The reasons for this will be brought out in an analysis of the cases of acute myocardial infarction in which necropsy was done. In some instances, elevation of the R-T segment was observed in lead I, in leads I and II (fig 2*D*) or in leads II and III (fig 2*H*), without a reciprocal depression in leads III and I, respectively. At times, especially in lead I, the R-T segment never rises above the iso-electric line (fig 2*A*), but there is a definite upward rounding of the segment preceding the shallow inversion of the T wave (fig 4*A*). If a tracing taken before an attack clinically suggestive of acute coronary occlusion is normal so far as the R-T segment is concerned, then this minimal change becomes highly significant. If further electrocardiograms disclose an increasing depth of the T wave and inversion and accentuation of the upward rounding of the preceding R-T segment, the so-called Pardee wave, then such a development practically establishes the presence of acute myocardial infarction. The evidence is further strengthened if, as the depth of the inversion of the T wave in lead I increases, T<sub>a</sub> becomes taller and more abrupt.

Lacking these changes which approach a definite electrocardiographic pattern of acute myocardial infarction, the clinical impression will be supported, though not conclusively, by an electrocardiogram showing progressive changes. These changes include the exaggeration of the T wave, followed by its depression or inversion, a change in voltage, usually consisting of a decrease, the appearance of a prolonged Q wave, especially significant in leads I and III, the appearance and disappearance of delay in conduction in either the auriculoventricular bundle or the bundle branches, and the occurrence of tachycardia paroxysmal in its onset and of auricular flutter or auricular fibrillation—any of which may occur during the course of an attack clinically suggestive of acute coronary occlusion.

Wilson and his associates<sup>36</sup> recently described certain changes in the initial deflections of the ventricular complex in association with myocardial infarction. They classified these changes under the headings of  $Q_1$  and  $Q_3$  types.

They found the  $Q_1$  type to be characterized by "the presence of a conspicuous and, in most instances, rather broad Q wave in lead I, the absence of Q in leads II and III, the small amplitude of the largest of the initial deflections in lead I, and the presence of a conspicuous S in leads II and III" (fig 2D).

The  $Q_3$  type is characterized by "the absence of Q in lead I, the presence of a conspicuous Q in leads II and III and the relatively small amplitude of the initial ventricular deflections in lead II" (fig 2E,F,G,H).

In a recent study<sup>37</sup> of the correlation of the  $Q_1$  and  $Q_3$  types of electrocardiograms, with the site of myocardial infarction disclosed at necropsy, a definite localizing value was found. A typical  $Q_1$  type of electrocardiogram is associated with acute or healing acute infarction in the anterior apical portion of the left ventricle and a typical  $Q_3$  type with acute or healing infarction involving the posterior basal portion of the same ventricle. In another study<sup>38</sup> of the Q and T types of electrocardiographic changes following acute myocardial infarction, it was found that the two types of changes had important complementary value. At some stage after acute coronary occlusion, either type may exist as the sole evidence of acute myocardial infarction, or both may be present simultaneously, with one more typical than the other. Only by the combined consideration of the Q and T types of changes will one derive the greatest assistance from the electrocardiogram in making the diagnosis of acute coronary occlusion.

Electrocardiograms taken with thoracic leads recently have been reported<sup>39</sup> to give information about acute myocardial infarction in addition to that obtained with the standard electrocardiographic leads. Evidence is submitted<sup>39</sup> that in infarction presumably involving the anterior and apical portions of the left ventricle the deviation of the

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36 Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L. The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* **16** 155 (June) 1933. Wilson, Barker, Macleod and Klostermeyer<sup>35</sup>

37 Barnes, A. R. Correlation of Initial Deflections of Ventricular Complex of Acute Myocardial Infarction, *Am Heart J* **9** 728 (Aug.) 1934.

38 Barnes, A. R. Q and T Types of Electrocardiograms. Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, *Am Heart J* **9** 722 (Aug.) 1934.

39 Wood, F. C., Bellet, Samuel, McMillan, T. M., and Wolferth, C. C. Electrocardiographic Study of Coronary Occlusion, Further Observations on the Use of Chest Leads, *Arch Int Med* **52** 752 (Nov.) 1933. Wood and Wolferth<sup>21</sup>

RS-T segment is likely to be more pronounced and lasting in the thoracic leads than in the standard electrocardiographic leads. No doubt this fact will be borne out in infarctions so situated, following which the electrocardiographic evidence in the standard leads consists almost entirely of the appearance of an inverted T wave in lead I, with the RS-T segment arising on or only slightly above the iso-electric line. In acute infarctions presumably involving the posterior portion of the left ventricle, the thoracic leads were less diagnostic than the standard leads. In only one instance of infarction in such a location did the thoracic lead furnish convincing evidence not shown by the standard leads. These observations are important and will lead to widespread clinical utilization. However, in my experience, if one is familiar with the changes in the initial and final ventricular complexes of the standard leads that constitute or approximate the classic changes of acute myocardial infarction, and particularly if the features in both complexes are studied in conjunction, the use of thoracic leads is required only in the rarest instances to clinch the diagnosis of acute myocardial infarction.

Whitten and I<sup>18</sup> studied the localizing value of  $T_1$  and  $T_3$  types of electrocardiographic changes. We found that a  $T_1$  type was associated with acute infarction of the anterior apical portion of the left ventricle and the  $T_3$  type with acute infarction involving the posterior basal portion of the same ventricle.

A number of observers have reported cases confirming the fact that the electrocardiographic changes in the RS-T segment following acute myocardial infarction have definite localizing value.<sup>40</sup> Wolferth<sup>41</sup> stated that he had not seen any case in which the electrocardiogram could have been classified as one or the other of the groups described by Whitten and me in which the situation of the infarct was not in the region predicted by our tables.

On the other hand, Gilchrist and Ritchie, in a very thoughtful article, questioned the localizing value of the electrocardiographic changes following infarction and called attention to a number of factors capable of distorting the ventricular complexes and thus of confusing the electrocardiographic pattern of acute myocardial infarction. These observers selected from the literature ten cases of coronary thrombosis,

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40 Bell, A., and Pardee, H. E. B. Coronary Thrombosis. Report of Two Cases with Electrocardiographic Localization of the Thrombus in the Right or Left Coronary Arteries, *J. A. M. A.* **94** 1555 (May 17) 1930. Rose, W. J., and Myers, Frank. Electrocardiographic Diagnosis of the Artery Occluded in Cardiac Infarction, *Proc. Soc. Exper. Biol. & Med.* **27** 681 (April) 1930. Wilson, Barker Macleod and Klostermeyer.<sup>35c</sup>

41 Wolferth, C. C. Diseases of the Heart and Blood Vessels, *Progres med.* **3** 109 (Sept.) 1931.

with the electrocardiograms and data obtained at necropsy. Analysis fails to indicate that their cases are in disagreement with localization on the basis of  $T_1$  and  $T_2$  types of electrocardiograms. Bundle branch block was present in two cases, and so prevented the classification of these two cases. In two cases of infarct in the anterior wall of the left ventricle and in one of infarct in the posterior portion of the left ventricle the electrocardiograms conformed to the patterns described by Whitten and me. The electrocardiogram in case 25 of their series was taken eighteen hours before death ("premortal"). This electrocardiogram suggests a  $T_1$  type, although it is not typical. The apex of the heart was thinned out, and microscopic examination of the region disclosed the presence of polymorphonuclear leukocytes and of small regions of necrosis suggestive of recent infarction. There was an ancient infarct in the left basal portion of the left ventricle. It seems likely that multiple infarcts were present in this case. In case 49 of their series, multiple infarctions were present. The exact relation of the recent septal infarct to the apex on the one hand, or to the posterior base of the left ventricle on the other, was not stated. In case 65 of their series, an infarct in the posterior basal portion of the left ventricle was present, and an elevated R T segment in leads I and II without S T depression in lead III is probably accounted for by acute fibrinous pericarditis<sup>42</sup> and the accumulation of 12 ounces (360 cc) of blood-stained effusion in the pericardium. In case 98 of their series, a curve was obtained that was in no way typical of infarction. The history suggests the occurrence of multiple occlusions. The electrocardiogram was premortal, being taken on the day of death. In case 112 of their series, the electrocardiogram taken fifteen days after occlusion showed Paidee T waves of  $T_1$  type. The infarction involved the apex and extended up over the posterior surface of the left ventricle. Acute apical infarction usually produces a  $T_1$  type of electrocardiogram.

Similarly, one may analyze four cases reported by Burton and his associates<sup>43</sup>. In case 1 of their series, infarction in the posterior basal portion of the left ventricle with a  $T_2$  type of electrocardiogram was present. In case 2, progressive congestive failure without a clinical history of angina pectoris or coronary thrombosis was present. Patchy fibrosis of the anterior part of the septum was found at necropsy. The electrocardiogram was not suggestive of infarction, and there was no

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42 Barnes, A. R. Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis, Report of Cases, *Am Heart J* **9** 734 (Aug) 1934.

43 Burton, J. A. G., Cowan, John, Kay, J. H., Marshall, A. J., Rennie, J. K., Ramage, J. H., and Teacher, J. H. Four Cases of Fibrosis of the Myocardium with Electrocardiographic and Postmortem Examinations. *Quart J Med* **23** 293 (April) 1930.

reason to expect that it would be, as the infarct presumably was of the chronic dystrophic type. In case 3, multiple regions of chronic fibrosis were present, one of which probably represented an ancient healed acute infarction and the others, areas of chronic dystrophic fibrosis. The electrocardiogram could not be expected to show changes, probably because it was taken too long after acute infarction had occurred. In case 4, there was no history of occlusion, but the first electrocardiogram is distinctly suggestive of subacute infarction in the anterior apical portion of the left ventricle. At necropsy, four months later, a healed acute infarct in this area was found. The two subsequent electrocardiograms, without evidence of myocardial infarction, simply represent the return to normal with healing of the acute infarct. These are not specious explanations of apparent discrepancies, they are explanations based on a knowledge of various factors which experiment and observation have led me to believe is correct.

In order to test the validity of the electrocardiographic criteria for determining the presence and site of acute myocardial infarction, I am reviewing all the cases of this type which have been seen at the Mayo Clinic in the past six years.

#### DATA ON ONE HUNDRED AND FIVE CASES OF MYOCARDIAL INFARCTION PROVED AT NECROPSY

These cases of infarction were classified in three categories

1 In the first category are fifty cases in which occlusion of a coronary vessel or acute myocardial infarction was discovered at necropsy. In seventeen the electrocardiographic findings accurately indicated the presence and site of the acute myocardial infarct or infarcts. In four of these cases the electrocardiograms were indicative of an infarction of the anterior and apical portion of the left ventricle, the location being confirmed at necropsy. In eleven of the seventeen cases, the electrocardiograms were characteristic of infarction in the posterior basal portion of the left ventricle with confirmation at necropsy. In two of the seventeen, acute infarctions of both the anterior apical and the posterior basal portion of the left ventricle existed, and a sufficient interval elapsed between these infarctions that the electrocardiogram could localize the infarctions in each portion. Reports of these two cases have been published previously (cases 2<sup>30</sup> and 3<sup>18</sup>).

In thirty-three cases, electrocardiographic evidence of myocardial infarction was not obtained, in eighteen no electrocardiographic tracing was obtained after the occurrence of acute coronary occlusion, in two bundle branch block occurred, preventing the appearance of the electrocardiographic changes of acute occlusion, and there were twelve instances in which multiple acute infarctions occurred. It has been

my associates' and my experience at the clinic that multiple infarctions, particularly if the anterior apical and posterior basal portions of the left ventricle are simultaneously involved prevent the appearance of the typical electrocardiographic signs of occlusion. This can be readily understood when one recalls that these two regions have opposing effects on the changes in the RS-T segment of the electrocardiogram. Therefore, the simultaneous involvement of these two areas produces mutually antagonistic effects which more or less completely neutralize the total effect on the RS-T segment. In one case in which acute coronary occlusion was complicated by acute pericarditis, elevation of the RS-T segment occurred in all leads, followed later by negativity of the T wave in all derivations (fig 6 *A,B,C,D,E*). A series of cases with this type of electrocardiographic change has been studied, and evidence has been submitted that this peculiar modification of the usual RS-T pattern may occur when acute coronary occlusion is complicated by pericarditis.<sup>42</sup>

2 In a second category of twenty-nine cases, necropsy revealed infarction which was classified as healed acute infarction. It is not always possible to distinguish this from the third type, classified as chronic dystrophic fibrosis. However, I have classified the second type as healed acute infarction when there was definite ancient occlusion of a vessel above the site of localized fibrosis, for example (*a*) when a localized fibrous replacement of the muscle resulted in aneurysmal dilatation, (*b*) when ancient pericarditis overlay an area of localized fibrosis of the myocardium, and (*c*) when a well organized thrombus underlay a region of more or less localized fibrous replacement of the myocardium. No history of acute coronary occlusion was obtained in sixteen of these twenty-nine cases, although that does not mean that such a history might not have been obtained in some by rigorous interrogation. Of the remaining cases, in all but three the history indicated that coronary occlusion occurred one year or more before the electrocardiogram was taken, in these three, occlusion occurred nine, five and two months, respectively, before the tracing was taken. There were two electrocardiograms in which relics of an acute occlusion were indicated, and in each instance the electrocardiograms accurately revealed the situation of the infarct. The remaining electrocardiograms gave no clue as to the previous occurrence of acute myocardial infarction. This probably can be accounted for by the fact that almost all the tracings were taken too long after acute occlusion had occurred.

3 Such cases of chronic myocardial infarction as did not fulfil the conditions imposed for inclusion in the second type were classified as instances of chronic dystrophic fibrosis. The third category comprised twenty-six cases. Complete or incomplete bundle branch block occurred



in six cases. The electrocardiogram in one case showed auricular flutter, and that in another, auricular fibrillation. The electrocardiograms in two cases were indeterminate because of poor tracings. In one case, low voltage of the QRS complex and T wave in all leads was indicated. In one case, the tracing showed an upward rounded ST segment in lead III, with a depressed ST segment in lead I. The infarction was incidental to extensive pathologic changes in the heart, consisting of subacute bacterial endocarditis superimposed on chronic rheumatic and aortic endocarditis with calcareous stenosis of the aortic valve. In nine cases, abnormal T waves were found in lead I or in leads I and II. It has been pointed out previously that if hypertension produces abnormal T waves, the abnormalities occur in those leads. It should be pointed out here, too, that the ST segment in hypertension is likely to have a certain pattern which is characterized chiefly by a depressed ST level in lead I or in leads I and II in conjunction with negative T waves in those leads. Such a change in the ST level must be distinguished sharply from the elevations of the RS-T segment suggesting acute infarction (fig 5 A,B,C). Finally, the tracings in five cases classified as instances of chronic dystrophic fibrosis were normal. It is the fashion when any type of RS-T change is observed in angina pectoris or coronary sclerosis to attribute that change invariably to coronary disease. Such a practice is unscientific and clinically unsound. Every clinician knows that there are numerous cases of angina pectoris and coronary sclerosis with or without chronic dystrophic changes in the myocardium in which the electrocardiograms are normal.

It is proved beyond doubt that acute coronary occlusion can produce modifications of the RS-T segment of the electrocardiogram. When coronary sclerosis produces delay in the conduction of the bundle branches, abnormal RS-T changes usually result. Definite transitory changes in the RS-T segments have been observed in some cases in which electrocardiograms were obtained during attacks of angina pectoris. But apart from these mechanisms, it has never been proved that coronary sclerosis, of itself, or even chronic dystrophic myofibrosis, can be held to account for modifications of the RS-T segment or of the T waves of the electrocardiogram. For this reason the "coronary T wave" should be designated the "coronary occlusion T wave." In the presence of angina pectoris and coronary sclerosis, other independent factors may be present and modify the RS-T segment and the T waves. Such factors are predominant ventricular strain,<sup>44</sup> most commonly due to hypertension, pericarditis or sudden pericardial effusion, myocarditis, toxic factors, particularly the results of digitalis therapy, and metabolic disorders, especially diabetic acidosis and myxedema. The

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44 Barnes, A. R., and Whitten, M. D. Study of T-Wave Negativity in Predominant Ventricular Strain, *Am Heart J* 5:14 (Oct) 1929.

presence of a great percentage of normal RS-T components in the electrocardiograms in cases of advanced coronary disease need assure no one of the absence of such a disorder, and conversely the presence of RS-T changes, except for the definite pattern seen following acute coronary occlusion, need lead no one to the easy conclusion that such changes necessarily are to be attributed to the presence of coronary sclerosis.

DATA ON ONE HUNDRED AND THREE CASES WITH A CLINICAL-  
HISTORY OF ACUTE CORONARY OCCLUSION NOT CONFIRMED  
AT NECROPSY

It must be admitted at the outset that the electrocardiogram of acute myocardial infarction, no matter how pathognomonic it is in the beginning, loses its absolute diagnostic value in from two to four weeks

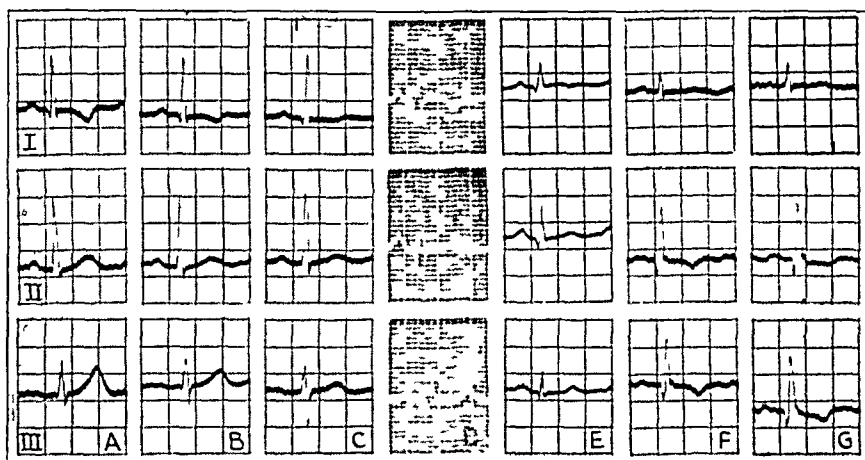


Fig. 4—Electrocardiograms showing residual changes of the  $T_1$  type taken (A) five weeks, (B) eleven weeks, (C) thirty-one weeks, (D) five weeks, and (E) three years and nine months, after acute coronary occlusion. Each tracing represents a separate patient, and typical electrocardiograms of a  $T_1$  type had been obtained of each patient in the first week after acute coronary occlusion. Tracings F and G were taken of a patient three months and three years and three months, respectively, after acute coronary occlusion. A tracing taken of this patient seven days after occlusion was typical of the  $T_2$  type.

after acute coronary occlusion. After that time, however, it may retain features highly suggestive of previous acute myocardial infarction in the form of Paidee's "coronary T waves." These waves are characterized by the origin of the R-T segment on or slightly above the iso-electric level and the upward rounding of the R-T segment and its termination in a sharp, deep T wave. Such waves, after acute infarction involving the anterior apical portion of the left ventricle, are seen in lead I or, rarely, in leads I and II (fig. 4 A, B, D). When the acute infarction involves the posterior basal portion of the left ventricle, the R-T segments of leads II and III take on the peculiar character described

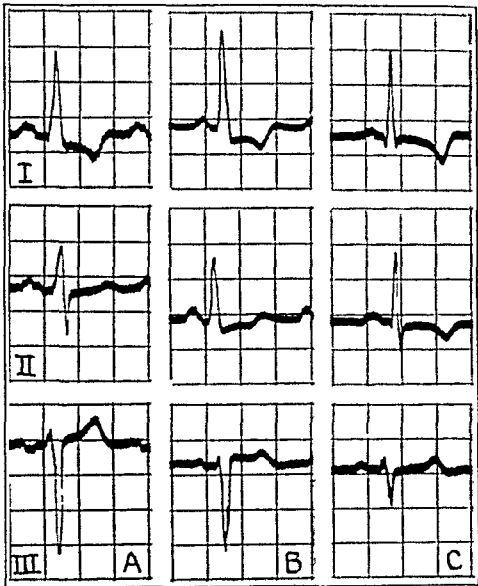


Fig 5—*A*, *B* and *C* show electrocardiograms taken of three patients who had marked essential hypertension but without coronary occlusion or myocardial infarction. The depressed ST segment in association with the negative T waves in the first lead may be contrasted with the iso-electric or slightly elevated RS-T segment of electrocardiograms of the  $T_1$  type obtained as a late relic of acute coronary occlusion.

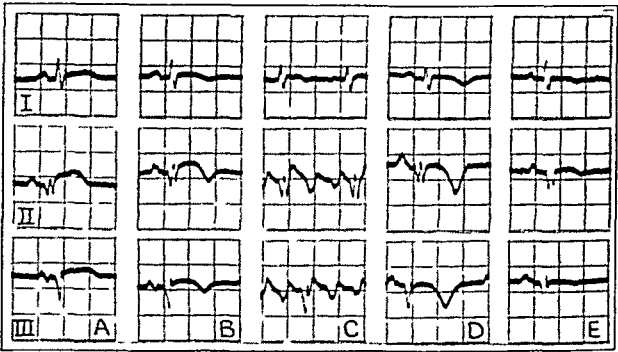


Fig 6—Electrocardiograms taken in a case of acute coronary occlusion complicated by pericarditis, taken (*A*) two days, (*B*) six days, (*C*) eight days, (*D*) twenty-one days and (*E*) four months, after the onset of the attack. Necropsy gave evidence of occlusion of the anterior descending branch of the left coronary artery with extensive healed acute infarction of the anterior and apical portion of the left ventricle. There was extensive chronic adherent pericarditis overlying the area of infarction.

by Paidee<sup>20</sup> Commonly, as  $T_1$  becomes deeply inverted  $T_2$  becomes upright, sharp and exaggerated, and the same happens to  $T_3$  as the  $T$  waves in leads II and III become deeply inverted Finally, shallow inversions of the  $T$  wave in lead I (fig 4E) or in the combined leads II and III (fig 4F,G), if the preceding R-T segment has remained isoelectric or slightly elevated, are often the last positive electrocardiographic evidence of relics of a previous acute infarction (fig 5)

Most of these patients recovered, those who died did not come to necropsy Only thirteen were seen within the first week after the acute occlusion

In only four of the one hundred and three cases were the electrocardiograms normal In these four cases tracings were taken three and a half, five, twelve and eighteen months, respectively, after acute occlusion In thirty-one cases tracings conforming more or less closely to a late type I pattern were found, in eight of these there were definite Q waves in lead I In thirty-four cases electrocardiograms belonging to a late type 3 pattern were found, in thirty of these there were prolonged Q waves in lead III, and both  $T_1$  and  $T_2$  types of electrocardiograms were observed in four cases in which multiple acute occlusions occurred Bundle branch and auriculoventricular block and auricular fibrillation and flutter comprised the electrocardiographic changes encountered in twenty-nine cases In only one case in the entire group in which frequent electrocardiograms were taken in the first three weeks after an attack clinically characteristic of acute occlusion did an electrocardiographic pattern characteristic of acute myocardial infarction fail to develop The pattern in this case did change, however, in that the  $T$  wave in lead III became negative, and a prolonged Q wave in lead III made its appearance Definite pericarditis occurred in this case The patient recovered so that multiple occlusions could not be excluded from the diagnosis, and absolute proof that infarction had occurred could not be obtained

The failures of the electrocardiogram to signalize myocardial infarction by changes in the RS-T segment were found to be explained by one of the following causes 1 Electrocardiograms were not obtained in sufficient number or in the proper time relation to the occurrence of acute myocardial infarction 2 There were multiple areas of acute myocardial infarction in the left ventricle 3 The presence of bundle branch block obscured the electrocardiographic pattern of infarction 4 Pericarditis or pericardial effusion modified the electrocardiographic changes 5 The amplitude of the deflections in lead I or lead II was so small that the RS-T changes characteristic of infarction could not be recognized 6 The tracing was taken of a patient who was dying

In the attempt to corroborate or refute evidence of relation between the  $T_1$  and  $T_2$  types of tracings and the situation of the infarct

in the heart, careful anatomic study of the heart must be made. The situation and size of the infarct should be recorded as accurately as possible. Search for multiple infarcts should be made, and if more than one is present they should be studied and described so as to establish their relative age, if they differ in that respect. A careful attempt to distinguish chronic dystrophic fibrosis from a healed acute infarction should be made according to the criteria laid down earlier in this article. The investigation of the myocardium must include microscopic as well as macroscopic study. In the average pathologic study of the heart, the anterior portion of the heart receives minute attention but the posterior basal portion is not studied as carefully. The presence of a large healed infarct in the anterior portion of the heart may lead the examiner to overlook a less obvious, but more recent, infarct in the posterior base of the left ventricle, this happened in a case recently reported<sup>36</sup> and led to serious question of the hypothesis of localization. Moreover, it must always be borne in mind that the more recent infarct dominates the RS-T changes in the electrocardiogram. Finally, in my experience, the electrocardiogram, by changes in the RS-T segment or T wave, apart from defects of conduction in the bundle branches, does not reflect the presence of chronic dystrophic fibrosis as it is defined in this paper, and therefore this type of fibrosis cannot be localized by any type of electrocardiographic changes described to date.

It is of interest to consider how soon after occlusion electrocardiographic changes indicative of occlusion may develop. The opportunity to obtain tracings within a few hours after occlusion is seldom afforded. In three of our cases in which acute infarction was proved at necropsy, electrocardiographic evidences of acute occlusion were observed within twelve hours. In four cases with clinical evidence of coronary occlusion but without proof at necropsy of acute myocardial infarction, the electrocardiographic pattern of infarction occurred within twenty-four hours. Cooksey and Freund recorded changes at one, two and three hours after acute occlusion, and Bell and Pardee published a report of a case with changes in six hours. Elkin and Phillips' patient showed early electrocardiographic changes of acute occlusion approximately ninety minutes after the severance of the anterior descending branch by stabbing. In our experiments with dogs<sup>19</sup> marked characteristic electrocardiographic changes were observed from twenty to thirty minutes after ligation of a coronary vessel. Wood and Wolferth<sup>21</sup> observed changes in the RS-T segment two minutes after clamping a coronary vessel in the dog. Thus it is apparent that electrocardiographic changes characteristic of infarction may occur in a few hours after acute coronary occlusion. In those cases in which the changes appear more slowly one suspects that occlusion took some time to

become complete or that the collateral circulation was sufficient to prevent a complete loss of anatomic and functional integrity of the muscle fibers in the area of infarction from occurring for some time. Certainly, tracings must be taken throughout the first week after acute occlusion before one concludes that the electrocardiogram of acute infarction failed to appear.

On the other hand, electrocardiographic changes of acute myocardial infarction may persist for a long time (fig. 4). In some of our cases the electrocardiogram showed a return to normal in three months, and in others it showed traces of the original abnormality for three years or more (figs. 4 *E* and *G*).

In a review of the literature as well as in a consideration of the cases forming the basis of this study, it was found that  $T_1$  and  $T_3$  types of electrocardiograms are about equally distributed in the cases in which recovery was made. The same is true of cases in which the patients died. Typical  $T_1$  or  $T_3$  types of electrocardiograms were encountered six times as often as atypical types in cases in which recovery was made. In the cases in which the patients died, atypical tracings of acute myocardial infarction predominated over typical tracings in a ratio of 4:3. This indicates that in the cases in which electrocardiograms after acute coronary occlusion show the closest approximation to the classic  $T_1$  or  $T_3$  pattern there is the best chance of recovery from the immediate attack. The atypical tracings frequently were found to be associated with multiple infarcts, with extensive single infarctions overrunning the localized regions of the heart, which yield the most characteristic electrocardiographic changes, or with infarctions complicated by pericarditis. This explanation derives support from some similar conclusions reached by Padilla and Cossio.<sup>45</sup> Low voltage of the QRS complex in all leads was encountered twice as often in cases in which the patients died of coronary occlusion as it was in cases in which the patients recovered. Its presence, therefore, appears to increase the gravity of the prognosis.

#### CONCLUSIONS

1. A knowledge of the coronary blood supply of the left ventricle is essential to an understanding of the problem of acute coronary occlusion.

2. It is essential to bear in mind that acute infarction involving the posterior basal portion of the left ventricle is approximately as common as is infarction of the anterior apical portion of that ventricle.

3. It is the situation of the acute infarct in the left ventricle and not the vessel supplying the area that determines the character of the electrocardiographic changes that will result.

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<sup>45</sup> Padilla, T., and Cossio, P. El electrocardiograma ventricular en el infarto miocárdico, *Semana med.* **36** 813, 1929.

4 Experimental ligation of vessels to the right and left ventricles of the dog produces electrocardiographic evidences of myocardial infarction that differ distinctly. Destruction of areas in the anterior portion of the left ventricle of the cat and of the dog produces electrocardiographic changes that are quite different from those obtained by the injury of similar portions of the posterior portion of the heart.

5 The characteristic feature of these electrocardiographic changes is a deviation of the RS-T segment.

6 Care must be exercised in interpreting the results of experimental ligation of coronary vessels to distinguish between the changes in the electrocardiogram produced by the pericardial reaction and those attributable to actual infarction of the myocardium.

7 The preponderance of evidence is against the interpretation that deviation of the RS-T segment in acute myocardial infarction depends on the development of an additional factor of cardiac failure.

8 Experimental and clinical evidence indicates that the RS-T deviation observed in the electrocardiogram after infarction is the primary event and that T wave changes are sequential and secondary to that deviation.

9 There is a definite pattern of RS-T changes characteristic of infarction in the anterior apical portion of the left ventricle and another indicative of infarction in the posterior basal portion of the left ventricle in the heart of man.

10 Although a constantly changing electrocardiogram observed after what is presumed to be acute coronary occlusion may be important corroborative evidence of that event, the degree with which these electrocardiographic changes approximate the  $T_1$  or  $T_2$  pattern will largely determine their worth in establishing the diagnosis of acute coronary occlusion.

11 Typically developed  $Q_1$  and  $Q_3$  patterns of infarction have a definite diagnostic and localizing value, and the combined consideration of the Q and T patterns will yield more information in the diagnosis than will either pattern considered alone.

12 Under proper conditions, the presence and situation of acute infarction can be predicted almost always from the electrocardiographic changes that develop. When changes in the electrocardiogram characteristic of acute myocardial infarction fail to develop, it will be found usually that tracings were not obtained in sufficient number or in proper time relation to the acute occlusion, multiple acute infarctions of the left ventricle were present, bundle branch block obscured the changes, pericarditis or pericardial effusion modified the electrocardiographic changes or the tracing was made at about the time of death.

13 Presumptive evidence of previous occlusion may be obtained from the appearance of inverted T waves observed months after the acute occlusion. These T waves are the coronary T waves of Pardee and are chiefly characterized by their depth and the character of the R T intervals that precede them. The reciprocal relation of  $T_1$  and  $T_2$ , in which as one becomes more inverted the other becomes more positive, is important evidence of preceding acute occlusion.

14 By no means are all RS-T changes observed in angina pectoris, coronary sclerosis or myocardial fibrosis to be ascribed to coronary disease.

15 Many cases of angina pectoris, coronary sclerosis and myocardial fibrosis present no significant electrocardiographic changes.

16 Neither the presence nor the situation of chronic dystrophic fibrosis of the myocardium is disclosed by any electrocardiographic change described to date.

17 Electrocardiograms with low voltage of the QRS complex in all leads after acute infarction probably increase the gravity of the prognosis.

18 The development of highly characteristic electrocardiograms of the  $T_1$  or  $T_3$  type after acute infarction seems to indicate a more favorable prognosis than do atypical electrocardiograms.

19 Electrocardiographic changes signifying acute infarction may appear as early as from one to two hours after acute coronary occlusion, and the electrocardiogram may not return completely to normal in some instances for two or three years or more.



# CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

## I CLINICAL EVALUATION OF STUDIES OF CIRCULATING BLOOD VOLUME

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AND

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The importance of a determination of blood volume in clinical medicine has long passed the experimental stage. Sufficient work has been done to prove that an abnormal blood volume will sometimes throw light on the underlying cause of a disease, and that it is helpful in the differential diagnosis of such diseases as hyperthyroidism, polycythaemia vera and cardiovascular disease, constituting a valuable aid in prognosis and treatment.

Some clinicians, however, still deny the importance of studies of blood volume on the ground that there is no accurate method of determining the circulating blood volume. It is admitted that from the exact physiologic standpoint, the methods utilized are not absolute, but, on the basis of an immense amount of work by others and our own observations in a large series of cases, we are firmly convinced that the results obtained justify the application of studies of blood volume to clinical medicine.

Our series comprised seventy-three subjects: ten normal persons, nine with hyperthyroidism, twenty-two with cardiovascular disease, five with compensated hypertension, seven with polycythaemia vera, six with anemia (varied), seven with metabolic disorders, one with avitaminosis (scurvy) and six with neurocirculatory asthenia.

### GENERAL TERMINOLOGY

Normally, the heart pumps out a certain amount of blood per unit of time from the ventricle into the periphery. This is known as cardiac output, minute volume or circulatory volume and is expressed in terms of liters per minute. The amount of blood ejected by the left ventricle with each systole is referred to as cardiac stroke, systolic output or

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From the medical service of Dr. Marcus A. Rothschild, and the Laboratory Department of Beth Israel Hospital.

stroke volume and is the result of the cardiac output divided by the cardiac rate. The amount of oxygen given up by a unit volume of blood to the tissues is known as the arteriovenous oxygen difference and is expressed in cubic centimeters of oxygen per liter of blood. This gives a measure of the relative activities of the circulatory and metabolic functions. The arteriovenous oxygen difference divided by the total oxygen content of the arterial blood gives oxygen utilization expressed in terms of percentage.

The amount of blood present in the organism is known as the total blood volume. This must be differentiated into two types. The part of the blood passing the heart once in the circulation is known as the circulating, active or rapid blood volume. The part moving slowly or passively, as through the liver, spleen, splanchnic areas or subpapillary plexus, is known as the stagnant or passive blood volume. Clinically, when the term blood volume is used, it generally refers to the circulating or active type.

Circulatory time is the shortest time that it takes a particle of blood or a foreign body to traverse the circulatory system from the peripheral veins through the heart and out to the other peripheral vessels. Venous pressure is the pressure residue in the vascular system after the resistance in the peripheral vessels (arterioles, capillaries and venules) is overcome.

#### BLOOD DEPOTS

*Spleen*—Whereas it is true that the various parts of the body that are called on to do the most active work need an additional supply of blood, this is not furnished by an increased frequency of rate or blood pressure, as was once thought, but by an increased stroke volume and cardiac output. The question that arises, then, is what is the source of the increase in circulating blood? The bone marrow does not produce red blood cells instantaneously nor can the tissues furnish the necessary fluid. Hence the increased supply of blood must come from certain areas where it is stored pending the time of need. In other words, there must exist in the body blood depots that are in readiness to supply blood to the tissues whenever this is necessary.

By blood depot is meant, to use Rein's<sup>1</sup> definition, an organ that is able to take up blood without affecting the nutritive or other needs of the concerned organ and without depriving the tissues of the body in general of their nutrition.

The existence of blood depots in the body was long suspected by physiologists, but there was no scientific demonstration of their exist-

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<sup>1</sup> Rein, H. Die Blutreservoirs des Menschen. *Physiologie, Klin. Wchnschr.* 12:1 (Jan. 7) 1933.

tence until the ingenious studies of Barcroft<sup>2</sup> and his associates made this possible. Barcroft noticed that there is a variation in the circulating blood when a person ascends mountains or passes through warm regions near the equator or through excessively cold zones. This so impressed him and his associates that they concluded that temperature must be an influential factor in the circulating blood volume. Carrying this theory into physiologic experiment, they compelled rats to inhale carbon monoxide and found that the gas quickly saturated the arterial blood of the rats, and that, if the animal was killed at the height of the poison, the splenic venous blood was free of the gas. They explained this phenomenon by the fact that the blood of the spleen is not in direct contact with the blood in the rest of the circulatory system. If the rats were permitted to run about while inhaling the carbon monoxide, the blood in the splenic vein was found to contain carbon monoxide, proving that during exercise the splenic blood participates in the general circulation. In short, the spleen is a blood depot, possessing the property of active muscular contraction, as well as expansion, so that it can expel into the circulation the blood that it hoards in its diverticulum-like spaces. In man, however, the musculature of the spleen is much less than that of the spleen of animals (dog), and so it is doubtful if contractility of this musculature is the sole factor in the unloading of hoarded blood from the spleen into the circulation. An additional, and probably far more important factor, would seem to be the influence of the vegetative nervous system on the spleen, as shown by the fact that stimulation of the vagus system (by means of the injection of choline) causes the spleen to hoard blood, whereas stimulation of the sympathetic system (by the injection of epinephrine) causes the spleen to contract and expel its noncirculating (hoarded) blood into the circulatory system.

*Liver*.—For some time, Barcroft and others thought that the spleen was the only blood-hoarding organ. Then it was noticed that after splenectomy there continues to be a variation in the blood volume during work and at rest, so that it was apparent that the body must have blood depots other than the spleen. Naturally attention was first directed to the liver, and experiments were successfully carried out to prove that the liver is a blood depot.

Rein demonstrated the vascularization of the liver by measuring, with the Stromuhr, the inflow through the portal vein and hepatic arteries and the outflow through the inferior and superior vena cava. He also showed that the liver can retain a large amount of blood and deliver it to the circulation in time of need without physiologic dis-

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2 Barcroft, J. J. Physiol. **73** 344, 1931.

turbance The blood of the liver constitutes 59 per cent of the weight of the blood-free organ, and of this, 39 per cent is active circulating blood and 20 per cent hoarded blood

Several theories have been offered to explain the way in which the liver acts as a blood depot Rein claimed that the expulsion of blood from it is a passive process, brought about by capillary dilatation and oozing Dale and his associates<sup>3</sup> agree that emptying is a passive process (that is, not produced by the action of its smooth musculature), but differed from Rein by stating that the organ empties by paralysis rather than dilatation of the capillaries Barcroft agreed that unloading is a passive action, but contended that it takes place by a change of capacity of the blood stream and is dependent on the capacity of the blood stream to dilate and contract Mautner and Pick<sup>4</sup> conversely claimed that the hepatic veins have a musculature, with contractile and dilation properties, and that it is the contraction and expansion of this musculature which causes closure of the central veins (*Venensperre*) sufficient to retain the blood that is to be hoarded and expansion thereof to discharge the hoarded blood in time of need Pick and Mautner showed that along the length of the branches of the central vein there is hypertrophy of the muscular walls which, under certain conditions causes throttling (*Grosseln*) of the blood from the liver These traction-like spaces which appear as small, converging vessels, form no closed mantle or covering, and can feed each other by acting as bolsters, increasing in width In the liver of man and carnivorous animals, such an arrangement of the musculature is to be seen in the region of the convergence of the smaller veins into the larger ones

*Subpapillary Plexus of the Skin*—Wollheim<sup>5</sup> showed that the subpapillary network, which is spaciouly situated between the end-capillaries and the subcutaneous tissue, can hoard as much as 1,800 cc of blood, or 30 per cent of the total circulating blood This has been confirmed by Barcroft and others The blood of the subpapillary plexus is not derived from the general circulation by a shunting process, as in the case of the spleen, but by a blockage process, a large quantity of blood being absorbed from the circulation through small apertures When filled, the subpapillary plexus contains slowly moving, stagnating blood, in contrast to the quick-flowing blood of the end-capillaries

<sup>3</sup> Bauer, W , Dale, H H , Poulson, L T , and Richards, D W J *Physiol* **74** 343, 1932

<sup>4</sup> Mautner, H , and Pick, E P *Arch f exper Path u Pharmakol* **97** 350, 1923

<sup>5</sup> Wollheim, Ernst Die zirkulierende Blutmenge und ihre Bedeutung fur Kompensation und Dekompensation des Kreislaufs, *Ztschr f klin Med* **116** 269 (April) 1931

*Lungs*—Hochrein and Keller<sup>6</sup> supported the theory that the lungs are a blood depot equal in importance to the spleen and liver. Rein, however, did not consider the lungs a real depot, but contended that the blood deposited there is the result of an alteration in the capacity of the blood stream. Change in capacity, he believed, is not identical with function as a depot. He admitted that there may be retention and expulsion of blood in the lungs owing to cardiac influence, but considered this different from hoarding. We agree with Hochrein and Keller that the lungs are hoarders of blood, though of less significance in this respect than the liver and spleen.

*Large Veins*—Whether or not the large veins hoard blood is still a matter of discussion. Gollwitzer-Meier<sup>7</sup> and Henderson and Harvey<sup>8</sup> expressed the belief that the large veins have a mechanism for hoarding blood and that it is one of musculature. Elias<sup>9</sup> studied the function of the musculature of the large veins in man by means of heat, cold and electric stimulation and showed that there is a marked narrowing of the musculature of the veins where the hepatic vein converges into the inferior vena cava. We are inclined to believe that the large veins do not play much part, if any, in the hoarding of blood.

#### METHODS AND TECHNIC

Although it has been possible to determine experimentally in animals during life the amount of blood hoarded by the various blood depots, it has obviously been impossible to determine this clinically in man. Attempts to determine the circulating blood volume in man as well as in animals have been successful, however. For this purpose various methods and technics have been devised, ranging from the direct method of bleeding animals and decapitation, as advocated by Welcker<sup>10</sup> in 1854, to the intravenous injection of physiologic solution of sodium chloride with ammonium oxalate, as advocated by Plesch,<sup>11</sup> in 1919. Grehant and Quinquaud,<sup>12</sup> in 1882, were the first to utilize carbon monoxide for determination of blood volume, and Kottman<sup>13</sup> was the first (in 1906) to try the intravenous injection of a foreign dye for determination of blood volume, using sodium indigotin disulphonate, U S P (indigocarmine), and methylene blue.

6 Hochrein, M., and Keller, J. *Arch f exper Path u Pharmakol* **164** 529, **166** 229, 1932.

7 Gollwitzer-Meier, K. *Venensystem und Kreislaufregulierung*, *Arch f d ges Physiol* **229** 264, 1931.

8 Henderson, Yandell, and Harvey, S. C. VIII. The Venopressor Mechanism, *Am J Physiol* **46** 353 (Aug.) 1918.

9 Elias, quoted by Eppinger<sup>21</sup>.

10 Welcker, H. *Blutkorperchenzahl und farbeproofende Methode*, *Vrtljschr f d prakt Heilk* **54** 11, 1854.

11 Plesch, J. *Haemodynamische Studien*, *Ztschr f exper Path u Therap* **6** 380, 1909.

12 Gréhant, N., and Quinquaud, E. *J de l'anat et physiol* **18** 564, 1882.

13 Kottman. *Arch f exper Path u Pharmakol* **54** 356, 1906.

It was not until 1915 that Keith, Rowntree and Geraghty<sup>14</sup> used colloidal dyes for the determination of the plasma and blood volume and established a method which, with various minor modifications, is now universally employed. By their method, a known amount of a nontoxic, slowly absorbable dye is introduced into the circulation to remain in the plasma long enough to become thoroughly mixed with it. The concentration of the dye in the plasma is determined colorimetrically by comparison with a suitable standard mixture of dye and serum, and the total circulating blood volume is computed by utilizing the hematocrit values.

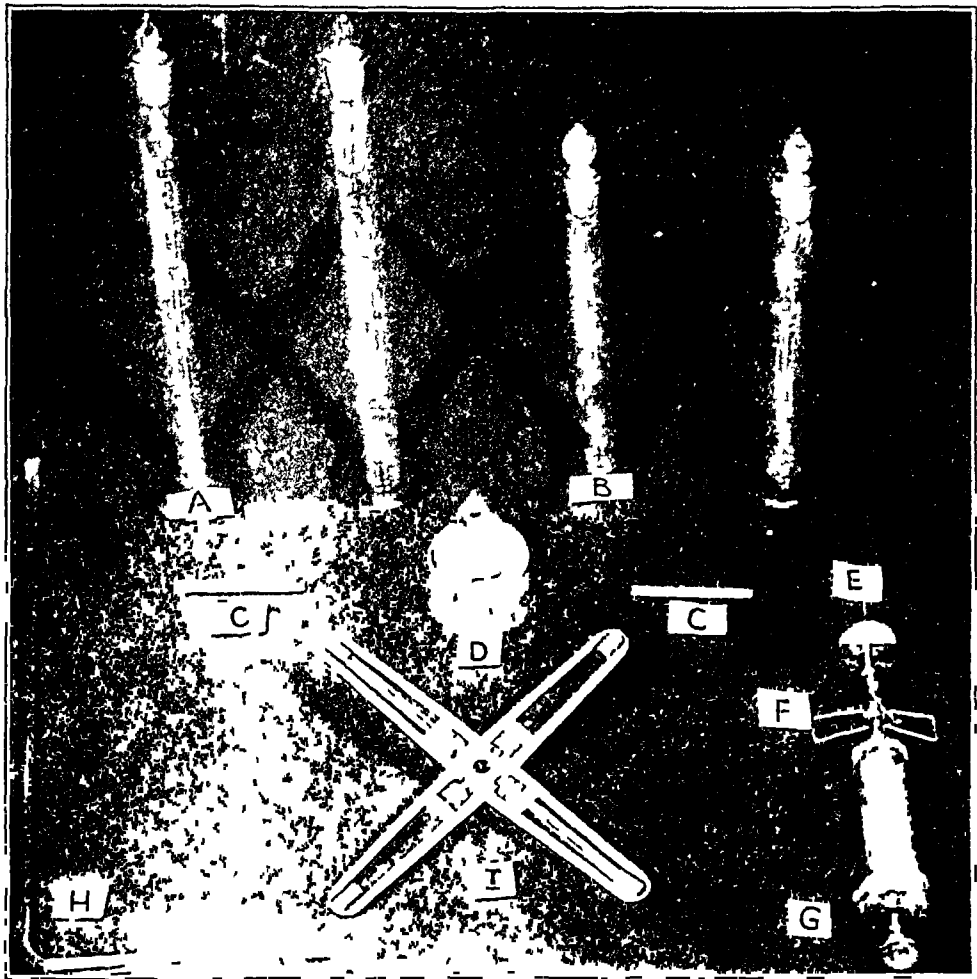


Fig 1—Apparatus used for determination of blood volume. *A* is a 15 cc graduate collecting tube, *B*, a 10 cc graduate collecting tube, *C*, hematocrit tubes, *D*, weight glass, *E*, cannula, *F*, Strauss connectors, *G*, 10 cc syringe, *H*, venous pressure tubing with adapter, and *I*, centrifuge holder for hematocrit tubes.

We have employed this method, with certain modifications, as follows:

The blood of the patient was taken either five or six hours after a light breakfast or after no breakfast, with the patient in a recumbent position for at least half an hour before the test. All material was sterilized before being utilized. *A*

<sup>14</sup> Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547, 1915.

large special cannula with a Strauss connection was employed for the withdrawal of blood into measured cylinders. As soon as the blood began to flow from the median basilic vein, the tourniquet was removed, and the hand was held open. No unnecessary pressure was exerted while blood was flowing. Two specimens of blood (15 cc each) were collected in this manner, to be utilized in making up a fresh standard for comparison (fig 1).

A solution of 10 cc of 0.6 per cent trypan red dye<sup>15</sup> was then injected into the patient's vein at body temperature, care being taken to wash away any of the dye remaining on the wall of the vein by pushing the piston of the syringe back and forth twice. Using a stop-watch, three minutes after the injection of the trypan red dye 10 cc of blood mixed with dye was withdrawn, and three minutes later a second amount of 10 cc was withdrawn.

While the cannula was in the vein, the venous pressure was determined. Right-angled glass tubing was attached to the cannula, with the arm of the patient resting flat on a pillow at the level of the auricle, and the rise of the blood column in the tube was noted (method of Taylor, Thomas and Schleiter<sup>16</sup>). The tube was removed, 0.25 cc of a freshly prepared 3 per cent solution of sodium cyanide was injected and, noting the time with a stop-watch, the first evidence of rapid or deep respiration with a sigh was recorded, which gave the pulmonary circulatory time (Robb and Weiss<sup>17</sup> method). We have also, recently, employed the glucoside method of Fishberg, Hitzig and King<sup>18</sup>.

The height, weight and age of each patient were noted, for a determination of body surface area. Vital capacity was determined by means of a Collins spirometer. The pulse rate and blood pressure were also noted.

To each of the four amounts of blood collected was added a 10 per cent solution of anticoagulant of the following mixture: ammonium oxalate, 2 Gm, sodium chloride, 0.8 Gm, and distilled water to make 100 cc.

From each of the two specimens of blood not containing dye, 1 cc was withdrawn to be utilized for a hematocrit determination (packed red blood cells). The remainder and the two samples of blood containing the dye were placed in separate centrifuge tubes and centrifugated for from thirty to forty-five minutes at a speed of 3,500 revolutions a minute to allow a separation of the blood into packed cells and plasma. The plasma levels were then separated into different test tubes.

Ten cubic centimeters of the plasma not containing dye was used to make up a fresh standard by adding to it and thoroughly mixing with it exactly 0.03 cc of trypan red dye solution (weighed in a special weight glass on an analytic balance).

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15 A fresh solution of trypan red was made daily as follows: 0.6 per cent trypan red added to 50 cc of physiologic solution of sodium chloride and 50 cc of distilled water were heated in a small beaker and stirred until the mixture boiled. This was filtered twice and distilled water added to bring the total amount to 100 cc.

16 Taylor, A. A., Thomas, A. B., and Schleiter, H. G. A Direct Method for the Estimation of Venous Pressure, *Proc Soc Exper Biol & Med* **27** 867 (May) 1930.

17 Robb, S. P., and Weiss, Soma. A Method for Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *Am Heart J* **8** 650 (June) 1933.

18 Fishberg, A. M., Hitzig, W. H., and King, F. H. Measurement of the Circulation Time with Saccharin, *Proc Soc Exper Biol & Med* **30** 651 (Feb) 1933.

This mixture constituted the standard for each patient, and the plasma containing dye was compared with it under a Duboscq colorimeter. The standard plasma not containing dye was placed in the left colorimeter cup at 20 on the scale division, and plasma containing dye was placed in the right colorimeter cup, after which five readings were taken for each specimen by two different observers (protocol) and the average determined.

The two centrifuge tubes, each containing 1 cc of blood not containing dye, were placed opposite each other in a special centrifuge and centrifugated at a rate of 10,000 revolutions a minute for thirty minutes. Then, the height of the packed cell column was read off directly in percentage from the hematocrit centrifuge tube, and the average of the two hematocrit values was utilized to determine the total circulating blood volume.

## EXAMPLE OF PROTOCOL

Date 1/20/32  
 Name Mr H G  
 Diagnosis Duodenal ulcer  
 Weight 57 Kg  
 Height 5 feet 9 inches (175.2 cm)

Surface area 1.67 square meters  
 Vital capacity 2,500 cc  
 Circulatory time (cyanide) 18 seconds  
 Venous pressure 12 cm

Amount of dye injected 10 cc  
 Standard 10 cc plasma plus 0.03 mg dye  
 Hematocrit reading 44, 41 Average, 44 ( $44 \times 11 = 484$  corrected [K])

Standard of Duboscq colorimetric reading at 10 mm

3 min specimen	6 min specimen		
11.2	10.8	$\frac{C_1}{C_2} = \frac{S_1}{S_2}$	
10.8	10.7		
10.8	10.9		
10.7	10.8	$\frac{100}{C_2} = \frac{10.6}{10}$	
11.2	10.9		
10.9	10.8		$S_2 = 92.6 (c)$
Average, 10.8			

$$\begin{aligned} \text{Total plasma volume} &= \left( \frac{100 \times f (P + a)}{a \times c} - f \right) \times \left( 1 - \frac{\frac{0}{(100 - K) \times b}}{100} + 0 \right) \\ &= \left( \frac{100 \times 10 (10 + 0.03)}{0.03 \times 92.6} - 10 \right) \times \left( 1 - \frac{\frac{2}{(100 - 48.4) \times 20}}{100} + 2 \right) \\ &= \left( \frac{1,000 \times 10.03}{2.778} = 3610.5 - 10.0 \right) \times \left( 1 - \frac{\frac{2}{(51.6 \times 20)}}{100} + 2 = 1 - 0.162 = 0.838 \right) \end{aligned}$$

$3,600.5 \times 0.838 = 3,016.8$  total plasma volume

$$\text{Blood volume} = \frac{100}{(100 - K)} \times \text{plasma} = \frac{100}{(100 - 48.4)} \times \text{plasma} = \frac{100}{51.6} \times \text{plasma}$$

$$1.93 \times 3,016.8 = 5,822.42 \text{ total blood volume}$$

$$\frac{3,016.8}{57 \text{ Kg}} = 52.9 \text{ cc plasma volume per kilogram}$$

$$\frac{3,016.8}{1.67 \text{ sq meter}} = 1,805 \text{ cc plasma volume per square meter of surface area}$$

$$\frac{5,822.4}{57} = 102.1 \text{ cc blood volume per kilogram}$$

$$\frac{5,822.4}{1.67} = 3,486 \text{ cc blood volume per surface area}$$

K indicates hematocrit value from blood volume cells (absolute volume of erythrocytes with dilutions considered), P, volume of oxalated plasma used for a standard, a, weighed volume used for dilution of the dye, b, volume of sample of dye, O, 1 cc + 1 cc of oxalate solution, c, reading of unknown against standard (percentage of dye against standard) and f, volume of injected dye solution.



## CRITIQUE OF METHOD

The question arises as to whether the dye method gives a sufficiently correct estimate of the total circulating blood volume to be of clinical value. We have found it to be the most reliable and adaptable of all infusion methods, it gives an exact determination of the circulating plasma volume, although not an absolutely exact determination of the circulating blood volume. However, by using hematocrit values, the circulating blood volume can be determined so accurately as to be of substantial clinical value. Absorption of the dye by the blood cells is entirely negligible, as shown by washing the cells. The following stipulations, however, must be kept in mind when utilizing the dye method to determine the total circulating blood volume. 1 The dye must be absolutely harmless. 2 There must be sufficient sojourn of the dye in the blood stream to permit its absorption by the plasma. 3 There must be equal diffusion of the dye through the blood. 4 The dye selected must be one that will not change in its chemical constituents in the blood stream, hence colloidal dyes are to be preferred.

## RESULTS

*In Normal Persons*—In the normal person we found that the plasma volume per kilogram of body weight varied from 36 to 49 cc, an average of 40.5 cc, and that the total circulating blood volume varied from 66 to 90 cc per kilogram of body weight, or an average of 78.4 cc. The hematocrit values varied from 36.5 to 50.5 cc with an average of 43.8 cc. The total circulating plasma volume averaged 2,780 cc, and the total circulating blood volume 5,386 cc. The pulmonary circulatory time by the Robb and Weiss method was between twelve and eighteen seconds, averaging sixteen seconds. Venous pressure values ranged from 3 to 5 cc, averaging 4 cc.

Comparing the values of our normal controls (table 1) with those of other authors (table 2) one notes the striking constancy of values obtained by the colloidal dye method. This is particularly noticeable in the values of the blood volume per kilogram of body weight. The carbon monoxide method, as utilized by Chang, is seen to give much lower values than those obtained by the colloidal dye method.

*Variation of Blood Volume Under Physiologic Conditions*—For the circulation to function properly, blood must be distributed to all the tissues, particularly to the tissues that are at work. The regulatory mechanism for this is more peripheral than central. The blood must be utilized as economically as possible as it passes through the tissues, so that there is a sufficient reserve in time of necessity. This is manifested by the correlation between the total circulating blood volume

TABLE 1—*Blood Volumes of Normal Adults in the Recumbent Position*

Number	Name	Sex	Body Weight, kg	Ideal Weight, kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg		Pulse Rate	Circulatory Time (Cyanide), seconds	Venous Pressure, Cmn
1	Thu	M	64.0	61.3	69	1.65	2,416	8.2	1,482	1,651	77.3	3,000	46.0	Systolic 110	Diastolic 69	75	11	1
2	Fle	M	68.0	68.0	71	1.87	3,369	49.0	1,862	3,625	82.0	3,008	36.5	110	70	68	12	5
3	Wel	M	71.0	71.8	71	1.89	2,866	40.3	1,511	6,412	90.7	3,463	50.5	100	70	72	18	1
4	Gin	M	72.7	72.7	69	1.74	2,915	40.0	1,675	5,532	79.0	3,041	43.0	100	80	73	17	1
5	She	M	57.2	63.6	66	1.62	2,425	42.3	1,499	1,851	84.9	3,000	45.0	110	70	70	16	5
6	Sha	M	63.1	58.1	63	1.65	2,709	42.9	1,639	5,036	79.6	3,052	42.0	110	80	76	17	1
7	Sus	M	85.4	60.4	64	1.90	3,162	37.2	1,664	6,000	70.2	3,159	43.0	100	80	68	18	0
8	Mur	M	70.0	65.9	67	1.80	2,533	36.6	1,407	4,709	67.2	2,616	42.0	100	70	68	17	1
9	Mor	M	63.6	66.3	66	1.68	2,717	43.1	1,635	5,004	78.6	2,978	41.0	80	65	76	17	1
10	Gru	M	72.7	66.3	68	1.81	2,633	36.0	1,438	5,713	78.0	4,121	49.0	110	70	78	21	1
Average			68.7	65.4	66	1.76	2,480	40.5	1,575	5,386	78.4	3,037	43.8	103	70	70	16	1

and the minute volume. If there is no correlation in the periphery, there may be poor utilization of the blood, so that there is an increase in the minute volume, hence an excessive demand on the central circulatory system, the heart and blood vessels. Because the minute volume shows how much blood is pumped out by the heart per minute, it may be considered a criterion of cardiac ability. The amount of minute volume is affected, among other factors, by functional variations in the amount of circulating blood volume and by the amount of blood emptied

TABLE 2—*Reported Average Values for Circulating Blood Volumes, Utilizing Carbon Monoxide or Dye Method*

Author	Method	Total Plasma Volume	Per Kg of Body Weight	Total Blood Volume	Per Kg of Body Weight
1 Chang, H. C., and Harrop, G. A., Jr J Clin Investigation 5: 393, 1928	Co			4,263	66
2 Ewig and Hinsberg, Ztschr f klin Med 115: 677, 1931	Co			4,700	73
3 Waterfield, R. L. J Physiol 72: 110, 1931	Co	2,950	41	5,244	71
Average for carbon monoxide method				4,735	70
4 Basok, M. I., and Shesterikova, T. I klin Med 22: 1076, 1931	Dye		40		74
5 Ernst, C., and Stagelschmidt, P. Ztschr f d ges exper Med 73: 678, 1930	Dye	2,945	40	5,340	80
6 Greisbach, W., in Bethe, A., von Bergmann, G., Emden, G., and Ellinger, A. Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 6	Dye	2,309	36	4,514	71
7 Martinez, Carrasco. Ztschr f klin Med 117: 540, 1931	Dye	3,415	57	6,112	100
8 Rowntree, L. G., Brown, G. E., and Roth, G. M. Volume of Blood in Health and Disease, Philadelphia, W. B. Saunders & Company, 1929	Dye	3,350	52	5,710	83
9 Ruznak, S. Deutsches Arch f klin Med 157: 186, 1927	Dye		44		82
10 Seyderhelm and Lampe. Ergebn d inn Med u Kinderh 27: 245, 1925	Dye		47		83
11 Uhlenbruch, P., and Vogels, S. Ztschr f klin Med 118: 172, 1931	Dye	2,700	42	5,650	79
12 Wollheim, Ernst <sup>5</sup>	Dye		40	5,336	80
Average for dye method				5,427	81
13 A. A. Goldbloom, I. Libin and P. K. Roht	Dye	2,780	40	5,386	78

into the heart during diastole (diastolic filling).<sup>19</sup> However, changes of blood volume do not follow corresponding changes of minute volume.

The yielding of blood in the capillaries to the tissues is dependent on the volume of blood in the capillaries, the pulmonary circulatory time and the composition of the blood. In a state of compensation, a minimum blood volume will circulate in normal circulatory time. The blood shows a compensatory state of polyglobulism, as evidenced by increased hematocrit readings, whereby more oxygen can be transported in a smaller amount of blood. At work, or after exercise, the fact of

<sup>19</sup> The results of our studies of cardiac output will appear in a separate publication.

sufficient circulation is evidenced by an increase in the circulating blood volume in a correspondingly increased circulatory time. The minute volume also increases if there is sufficient reserve force in the heart. When there is no correlation between the minute volume expelled by the heart and the circulating blood volume, a hemodynamic disturbance of necessity manifests itself.

Studies have been carried out by a number of workers to determine the influence of various factors on the circulating blood volume. The factors fall mainly into three general groups: hematogenous, pharmacologic and humoral. Some of the factors causing a physiologic increase in the blood volume are: hematogenous, including low atmospheric pressure (lessened oxygen pressure) and inhalation of carbon dioxide; pharmacologic, including epinephrine, barium chloride, caffeine, camphor, strychnine sulphate, pituitary extract and thyroid extract; and humoral, e. g., exercise. Some of the factors causing a physiologic decrease in the blood volume are: hematogenous, including high atmospheric pressure (heightened oxygen pressure), diets poor in salt and nitrogen and increased inhalation of oxygen; pharmacologic, including digitalis, histamine, morphine and peptone; and humoral, comprising postoperative shock, sitting or standing posture and sleep.

*Alterations in Blood Volume Due to Pathologic Factors*—Hyperthyroidism. Nine cases of hyperthyroidism were studied, and the average total circulating blood volume was found to be one and a half times greater than that of normal persons. The increase in the circulating blood volume corresponded with an increase in the plasma volume. The hematocrit values were slightly increased, and the circulatory time (twelve seconds) was more rapid than normal. The venous pressure, however, was within normal range (table 3).

It is usually assumed that increased circulating blood volume is a compensatory mechanism because of increased consumption of oxygen, as evidenced by an increased basal metabolic rate. However, we noted that whereas under therapy with compound solution of iodine the basal metabolism is diminished there need not be a simultaneous effect on the circulating blood volume. The latter may diminish much later than the basal metabolic rate. It is possible that the increase in blood volume in our cases was governed by a special hormonal effect of the thyroid activity on the spleen, causing an outflow of blood hoarded in that depot. The forcing of such hoarded blood, with its corpuscular elements into the blood stream would serve to explain the absence of anemia and the presence of lymphocytosis in thyrotoxicosis.

All of these patients were slightly underweight and their blood pressure showed, on the average, only a moderately increased systolic value and a normal diastolic value, giving increased pulse pressure. The

TABLE 3—Blood Volumes of Patients with Hyperthyroidism Before Operation

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Ideal Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg	Systolic	Diastolic	Pulse Rate	Clrenulatory Time (Cyanide), Seconds	Venous Pressure, Cmm	Basal Metabolic Rate
11	Gor	F	55.0	62.2	64	1.57	2,721	50.5	1,765	7,481	130.0	4,794	120.2	58.5	130	80	96	10	7	+	+41
12	Hef	F	46.0	52.7	60	1.47	2,659	56.8	1,967	7,454	110.0	4,604	97.8	44.0	130	70	84	15	0	+	+44
13	Nac	F	61.3	55.9	60	1.55	3,431	50.0	2,213	6,347	104.0	4,604	113.1	42.0	115	70	88	18	1	+	+26
14	Gee	F	51.6	60.0	61	1.41	2,773	51.7	1,966	4,915	95.2	3,485	81.9	40.0	128	68	88	16	5	+	+40
15	Iev	F	38.5	55.9	59	1.28	2,335	63.0	2,058	4,690	121.0	3,664	83.8	40.0	140	80	88	13	6	+	+20
16	Wor	M	53.6	67.2	67	1.62	3,645	68.0	2,270	6,510	121.4	4,018	96.8	40.0	130	80	108	9	1	+	+30
17	Shl	M	55.0	68.1	65	1.63	3,275	59.5	2,009	6,486	117.9	3,979	95.2	45.0	129	60	120	10	6	+	+70
18	ShH	M	52.0	60.0	64	1.53	3,109	60.0	2,032	6,714	129.0	4,407	112.4	49.0	140	80	123	10	8	+	+60
19	Sta	M	66.0	73.1	69	1.66	3,238	49.0	1,947	6,018	91.1	3,622	82.3	42.0	138	70	110	11	8	+	+42
Average			53.2	61.6	64	1.51	3,059	58.0	2,023	6,058	114.2	3,981	98.1	44.5	130	73	100	12	6	+	+41

TABLE 4—Blood Volumes in Patients with Cardiovascular Disease with Decompensation Showing High Values (So-Called Plus Forms of Decompensation)

Number	Name	Sex	Body Weight, kg	Ideal Weight, kg	Height, inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each kg of Body Weight	Cc for Each Sq M of Body Surface	Ideal Body Weight of Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm	Comment
20	Col	M	61.5	62.7	61	1.44	2,702	55.8	1,922	7,336	138.2	3,603	117.0	200	140	21	24	Decompensation, hypertension, orthopnea, edema
21	Tin	F	61	62.6	61	1.57	2,607	42.5	1,660	8,472	138.2	3,000	135.3	150	80	27	24	Decompensation, hypertension, orthopnea, edema
22	Hab	F	37.7				2,055	54.7		4,440	119.0		49.0	118	70	76	18	Dyspnea, edema of feet, cyanosis, cor pulmonum
23	Sch	M	81.3				3,619	44.5		7,527	92.5		47.5	120	100	108	24	Dyspnea, general edema, anasarca, fibrillation, chronic coronary disease, loss of 20 pounds (12.2 kg) after operation
24	Shr	M	59.0	62.5	62	1.58	3,518	60.6	2,390	6,352	107.3	4,221	101.3	200	136	92	11	Dyspnea, cyanosis, decompensation, hypertension, coronary thrombosis, mesenteric lymph nodes
25	Mis	M	54.0	64.5	65	1.57	3,223	60.0	2,032	6,247	115.0	3,980	96.8	196	108	88	15	Decompensation, hypertension, edema, dyspnea
26	Hal	F	70.0	67.7	65	1.75	3,128	44.7	1,787	6,477	92.5	3,701	95.6	166	104	88	13	Decompensation, coronary disease
Average			58.9	64.0	62	1.58	2,988	51.8	1,961	6,690	115.9	4,479	109.2	171	105	90	19	

average basal metabolic rate was plus 41. The fact that in many of the patients there was no hypertension indicates that the presence of hypertension is not necessary to an increase in blood volume.

**Cardiovascular Disease** Twenty-two cases of cardiovascular disease were studied (table 12), and the average blood volume determination was 95.9 cc per kilogram of body weight. However, the twenty-two cases fall into two groups: seven showing an increased blood volume, averaging 115.9 cc per kilogram of body weight (table 4) and fifteen showing a decreased blood volume, averaging 71.4 cc per kilogram of body weight (table 5).

When there is no correlation between the minute volume expelled by the heart and the circulating blood volume, the clinical manifestations of the resultant disturbance are those of decompensation. Wollheim<sup>20</sup> classified two types of compensation, the "plus" and the "minus" forms, each group being determined by whether or not the blood volume is increased or decreased.

The average for our cases with the plus form of decompensation showed that this group had the greatest circulating volume in the series with the exception of the cases of polycythaemia vera (fig. 2). The high figures in the group with the plus form of decompensation were determined by an increase in both the plasma volume and the hematocrit determination (50 per cent of packed cells in the blood) in contradistinction to the figures for the cases of polycythaemia vera which showed a normal plasma volume and a very high hematocrit value (67.5 per cent of packed cells in the blood). The cases with the plus form showed a high venous pressure and high blood pressure, with a tendency toward symptomatic polycythemia. The cases studied were of the essential hypertensive type, showing left ventricular failure, chronic disease of the coronary artery and organic arteriosclerotic valvular (aortic or mitral) disease. The clinical survey of these patients generally revealed wakefulness, restlessness, dyspnea, which was lessened if the patient sat with the legs hanging down over the edge of the bed, cyanosis of the prominent bony areas, greatly filled veins in the neck, the filling increased by pressure on the liver and increased blood volume. The cause of the cardiac disturbances in most of the cases was overwork and arrhythmia.

When one follows the improvement of the patient with the plus form of decompensation, with increased blood volume and venous pressure and prolonged pulmonary circulatory time under rest or therapy, it is noticed as a state of compensation is reached the blood volume and venous pressure diminish and the circulatory time returns to normal. Correspondingly, the patient with the minus form of decompensation in

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20 Wollheim, E. *Klin. Wchnschr.* 12:12 (Jan. 7) 1933.

TABLE 5—Blood Volumes in Patients with Cardiac Disease with Decompensation Showing Low Values (So-Called Minus Forms of Decompensation)

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cc for Each Kg of Ideal Body Weight	Cells by Hem to Crit, per Cent	Blood Pressure, Mm of Hg	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cmn	Comment
27	Din	M	71.0	66.0	70	1.75	3,169	44.5	1,826	6,455	69.0	2,698	97.8	46.0	170	70	14	18	Dyspnea, edema, heart block
28	Kle	M	63.6	66.0	70	1.71	2,555	44.9	1,669	4,365	69.8	2,552	109.1	32.0	130	70	9		Rheumatic fever, endocarditis, heart block, mitral stenosis
29	Gol	M	80.0	75.0	69	1.89	3,082	38.5	1,650	6,240	78.0	3,401	83.2	46.0	140	75	9		Chronic decompensated auricular fibrillation, orthopnea
30	Per	F	60.0	62.7	62	1.58	2,407	40.1	1,523	4,337	72.2	2,744	69.1	40.5	120	80	10		Auricular fibrillation, edema of the liver, recurrent cardiac disease
31	Cha	F	74.5	62.7	62	1.75	2,832	38.0	1,605	4,605	61.8	2,631	75.4	35.0	112	60	21		Acute attack of coronary failure intraventricular block, chronic cardiac disease, hypertension for 3 years
32	Lps	M	82.0	70.4	67	1.89	2,697	33.0	1,370	4,496	54.8	2,715	63.8	46.0	200	140	5		Recurrent cardiac disease, intraventricular block, fresh coronary closure, large liver
33	Hur	M	65.0	70.4	67	1.70	2,701	39.8	1,724	5,132	79.0	3,018	72.8	45.0	120	50	3		Orthopnea and dyspnea (7 weeks) cyanosis, protodiastolic murmur, liver 2 fingerbreadths below costal margin, chronic cardiac disease
34	Kra	M	66.3	65.9	64	1.69	2,471	36.9	1,470	4,714	71.1	2,786	71.5	45.0	116	112	12		Rheumatic fever, endocarditis
35	Gre	F	59.0	60.0	66	1.65	2,627	44.0	1,591	5,201	88.0	3,152	86.6	45.0	112	60	80	10	Decompensation, hypertension, jaundice, diabetes
36	Mis	M	63.0	61.3	62	1.61	2,673	42.4	1,641	4,143	65.7	2,533	67.5	36.0	170	100	13		Orthopnea, pulmonary edema (chronic cardiac disease, renal coronary closure)
37	Bar	M	70.0	70.3	66	1.77	2,422	34.6	1,368	5,176	73.9	2,924	73.6	48.0	96	64	25		Acute rheumatic fever with pericarditis
38	Sel	M	50.0	58.1	64	1.50	2,216	44.3	1,477	4,486	89.7	2,990	77.2	46.0	140	70	15	19	Batton hole mitral stenosis, or
39	Bra	M	55.0	65.1	65	1.58	2,617	47.1	1,656	4,966	89.6	3,079	76.2	43.0	125	70	17		thoracic edema, prominent venous pulsations, large liver, auricular fibrillation
40	Lml	M	72.0	61.2	65	1.74	1,822	25.0	1,017	3,255	44.0	1,807	53.1	40.0	140	80	15		Rheumatic fever
41	Jon	M	66.8	66.1	66	2.05	2,610	27.0	1,251	5,244	54.1	2,521	70.3	46.0	171	140	55	17	Orthopnea and dyspnea (1 year's) general edema, scrotal edema, hypertension, heart palpitation, loss of 36 pounds
Average			68.5	65.4	65	1.72	2,606	38.6	1,599	4,854	71.4	2,832	74.0	42.0	147	83	25	12	



a state of compensation shows an increase of the blood volume to a normal level, a normal circulatory time and a venous pressure that drops to normal in the majority of cases

In the fifteen cardiac cases showing a decreased circulating blood volume, there was a tendency toward increased venous and blood pressure. The finding of a decreased blood volume per square meter of surface area was due to the diminished plasma volume and a normal hematocrit value. The majority of the patients were subject to recurrent rheumatic attacks, of either rheumatic endocarditis or rheumatic mitral disease, with or without auricular fibrillation. In a minority of the cases there was normal venous pressure (Mis, Har, Eps, Gol and Kle), and the patients presenting cyanosis and orthopnea gave the clinical impression of belonging to the group with the plus form of decompensation. However, they had, respectively, the following blood volumes per kilogram of body weight: 65.7, 79, 54.8, 78 and 61.4 cc (table 5).

It is interesting to note that Bar, a patient with chronic disease of the coronary artery with left ventricular failure, should have shown a much higher circulating blood volume than 73.9 cc per kilogram of body weight, taking into consideration also his decompensated state. However, there developed an acute coronary attack, during which he died, and it was this attack which produced the low circulating blood volume, although it did not fall to the level of the diminished blood volume in cases of shock or collapse. It is more than suggestive of these cases that coronary occlusion may be suspected when a diminished or low normal blood volume is encountered in patients in a state of decompensation with a previous history of left ventricular failure and hypertension, and presenting symptoms of orthopnea and dyspnea. The observations on venous pressure cannot be conclusive, because there is no increase or decrease in pressure simultaneous with the increase or decrease of the circulating blood volume.

In contradistinction to Bai, Sei, who had acute rheumatic fever with pericardial effusion, showed an increased blood volume and venous pressure, although one would have expected to find a low blood volume and a low venous pressure. This anomaly was explained, also, by observations at autopsy, which showed that adherent pericarditis had caused poor emptying of the left ventricle of the heart with increased pressure in the venous system and in the lesser circulation.

Clinically, the minus form of decompensation generally presents the following symptoms and signs: fatigue, drowsiness, dyspnea and orthopnea, lessened in a reclining position, cyanosis of the body and extremities, poor filling of the veins of the neck, not increased by pressure on the liver, and decreased circulating blood volume. The etiologic factor is generally arrhythmia, recurrent infections (such as endocarditis,

grip and angina) or chemical toxins, giving a sympathicotonic (vasomotor) effect

The effect of infections on the circulating blood volume is due to increased protein decompensation which may be compared to the effect of peptone and histamine, which diminish the circulating blood volume. The dynamics of the minus form of decompensation begin with the opening of the capillary depots and the absorption of blood from the circulation. The circulating blood volume and the minute volume diminish simultaneously, owing to the lessened capacity of the veins and to the diminished diastolic filling of the heart due to the poor return of the venous blood. Clinically, patients with the minus form of decompensation show a similar effect of toxins on the capillaries, that is, there is a paralysis of the vasomotor centers causing vasomotor collapse.

It is important to differentiate clinically the cases of chronic cardiac disease showing a minus form of decompensation from cases of acute peripheral failure, as evidenced by shock and collapse. This is not true, however, except when there is acute coronary thrombosis and actually postoperative collapse. The differential points between the minus form of decompensation and vasomotor collapse are, briefly

"Minus" Decompensation	Vasomotor Collapse or Shock
Chronic many days to weeks	Acute, minutes to hours
Poor blood supply from dilated capillary depots, but arteriole tone present	Tone of splanchnic arterioles diminished
No drop in blood pressure	Marked drop in blood pressure
Blood volume moderately diminished	Blood volume markedly diminished
Venous pressure usually diminished, but may be increased	Venous pressure always markedly diminished, sometimes to an indeterminate point

**Hypertension (Compensated)** In the group of five patients with compensated hypertension we included those suffering from hyperthyroidism, essential hypertension, basophilic adenoma with hypertension and anemia. From our observations it appears that hypertension itself has no effect on the circulating blood volume, as it was either normal or at most only slightly diminished in all the cases in the group (table 6). When decompensation sets in, however, the blood volume is affected, the third greatest increase was noted in patients suffering from hyperthyroidism, but in most there was no hypertension. This condition disposes the patient to an increased blood volume, but since hypertension is not always present it is apparent that the increased blood volume is not a factor predisposing to hypertension.

**Polycythaemia Vera** Seven patients presenting a severe form of polycythaemia vera were studied (table 7) and were found to have an increased total blood volume per kilogram of body weight and a high increase in hematocrit value. The average plasma value was somewhat

TABLE 6—Blood Volumes in Compensated Hypertension Cases

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cells by Hemato crit, per Cent	Systolic Blood Pressure, Mm of Hg	Diastolic Blood Pressure, Mm of Hg	Pulse Rate	Circulatory Time (Cyanide) Seconds	Venous Pressure, Cm	Comment
42	Pop	F	57.0	62.7	69	1.96	2,727	47.9	1,748	5,401	94.7	3,462	45.0	160	110	98	15	7.5	Diabetes mellitus
43	Pen	F	45.4	61.5	69	1.46	3,075	67.5	2,106	5,000	110.1	3,424	35.0	186	56	100	15	10.0	Thyroid disorder, diabetes, hypertension, inemia
44	Wru	F	61.0	62.7	62	1.60	1,941	31.8	1,213	3,929	64.4	2,455	46.0	208	130	88		6.0	Basophilic adenoma
45	Ble	M	70.0	60.4	61	1.71	2,603	37.2	1,522	4,840	69.2	2,870	42.0	165	100	86	10	8.0	Hypertension
46	Kor	M	71.8	61.3	62	1.71	2,585	36.0	1,505	5,010	69.7	2,929	44.0	205	120	96	16	7.0	Hypertension
Average			61.0	62.7	62	1.60	2,586	44.0	1,618	4,896	81.6	3,020	42.4	190	103	90	13	7.7	

TABLE 7—Blood Volumes in Cases of Polycythæmia Vera

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cells by Hemato crit, per Cent	Systolic Blood Pressure, Mm of Hg	Diastolic Blood Pressure, Mm of Hg	Pulse Rate	Circulatory Time (Cyanide), Seconds	Hemoglobin, per Cent (Sph)	Red Blood Cells per Million
47	Tha	F	54.0	67.3	59	1.57	2,620	48.1	1,693	12,776	212.0	8,010	186.8	130	70	82	18	129.0	8,069
48	Bro	M	60.2	67.3	64	1.62	1,900	50.0	1,907	10,482	174.0	6,483	163.7	145	80	80	24	100.0	5,800
49	Day	F	54.0	67.3	65	1.57	2,774	50.3	1,741	6,734	124.0	4,289	160.5	120	65	72	19	102.0	5,800
50	Mei	M	52.0	65.9	65	1.55	1,962	35.8	1,264	8,531	164.0	5,503	129.4	140	80	80	17	123.0	8,000
51	Hac	M	63.6	70.4	67	1.70	2,130	33.4	1,232	8,493	132.9	4,910	120.0	140	90	80	4	123.0	9,100
52	New	M	63.6	63.6	63	1.53	1,930	36.0	1,261	11,772	219.9	7,629	185.0	160	110	92	12	123.0	10,000
53	Mes	M	67.2	60.0	60	1.48	2,820	41.9	1,905	8,571	127.5	5,791	142.8	145	95	70	20	107.0	7,700
Average			57.9	65.9	64	1.57	2,475	42.2	1,571	9,589	167.7	6,090	141.7	140	84	78	18	115.8	7,840

TABLE 8—Blood volumes in Cases of Anemia (Varied)

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Ideal Body Weight of Cc for Each Kg of	Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pres sure, Cm	Hemoglobin, per Cent (Sahl)	Red Blood Cells per Million	Comment
															Systolic	Diastolic						
54	Gol	M	67.2	59.3	69	1.62	3,825	49.9	1,910	3,789	6.1	2,411	87.3	24.0	115	70	96	13	18.1	30.0	2,500	Anemia, myxedema
55	Ste	M	67.9	53.4	72	1.65	3,241	49.0	1,978	4,661	7.8	2,624	90.0	22.0	125	75	88	14	4.5	1.0	2,600	Gaucher's disease spleen much enlarged
56	Kle	M	60.0	59.0	61	1.57	2,999	49.9	1,910	3,789	6.1	2,411	84.2	19.0	100	70	84	11	1.5	48.0	2,000	Pernicious anemia
57	Bru	M	53.6	50.0	64	1.54	2,918	55.6	1,999	4,598	86.0	2,585	77.5	22.0	125	70	90	11	8.0	40.0	1,000	Meloblastic leukemia
58	Ros	M	63.6	64.0	66	1.68	2,444	84.1	1,431	4,280	67.2	2,548	66.9	9.0	120	80	78		5.0	51.0	3,770	Splenomegaly leukemic
59	Rei	M	66.3	55.1	78	1.85	3,255	49.1	2,060	5,489	82.7	3,471	99.8	27.0	100	85	75		8.0	52.0	3,700	Anemia (immense)
Average			64.1	58.6	69	1.60	3,123	49.8	1,977	4,720	71.9	2,619	81.0	20.0	124	74	81	13	8.0	42.5	2,600	Wassermann + plus

TABLE 9—Blood Volumes in Cases of Metabolic Disorders

Number	Name	Sex	Body Weight, Kg.	Ideal Weight, Kg.	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Ideal Body Weight of Cc for Each Kg of Body Weight	Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg		Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cms	Obesity	Diabetes	Obesity, subcutaneous	Disturbance of thyroid	Obesity, hypertension	Cirrhosis of the liver	Myxedema	Nephrosis
															Systolic	Diastolic											
60	Hal	M	127.0	57.2	99	2.10	2,916	26.4	1,401	3,665	64.5	2,840	8.5	49.0	115	80	99	16	5								
61	Wra	M	100.0	97.2	99	1.72	2,119	21.4	1,267	3,785	73.7	2,490	91.2	40.0	95	70	70	16	1								
62	Ros	M	100.0	97.2	99	1.72	2,916	26.4	1,401	3,665	64.5	2,840	8.5	49.0	115	80	99	16	5								
63	Ian	M	92.7	65.5	95	1.97	3,293	35.3	1,671	6,553	69.6	2,819	94.7	50.0	210	75	80	13	8								
64	Cole	M	63.0	70.0	64	1.68	2,273	36.0	1,371	3,681	66.2	2,490	81.2	74.0	110	80	70	21	5								
65	Wra	M	85.0	70.0	64	1.68	2,273	36.0	1,371	3,681	66.2	2,490	81.2	74.0	110	80	70	21	5								
66	Nov	M	65.0	61.3	63	1.49	3,210	46.1	1,922	5,662	75.5	2,744	91.7	50.0	120	80	80	15	1								
Average			83.2	63.8	64	1.84	2,972	46.6	1,589	5,661	68.5	2,600	88.8	42.1	125	83	71	15	8								

less than normal and considerably less than in many other conditions. The venous pressure and circulatory time were normal except in the case of Bar, who showed decompensation.

In symptomatic polycythemia we found that the total blood volume is diminished and that the plasma volume is diminished or normal, while the number of erythrocytes and the hematocrit value are high, producing a state of polycythaemia normovolemia. In polycythaemia vera, on the other hand, the cell volume and blood volume are markedly increased, producing a volume status of polycythaemia hypervolemia. Although there was marked increase in the viscosity of the blood and a tendency to sluggish circulation, the circulatory time was actually only slightly affected. The main differentiating point was the high hematocrit value in polycythaemia vera.

**Anemia** Six cases of anemia were studied, which included the following conditions: myxedema, Gaucher's disease, pernicious anemia, myeloblastic leukemia and splenomegalic anemia (table 8). When the total blood volume was normal, the blood volume per kilogram of body weight remained in the lower levels of normal. One wonders whether the mechanism that causes the increased plasma volume is not a compensatory or adaptive one, that is, a replacement factor.

**Metabolic Disturbances** In the group of seven patients showing clinical manifestations of obesity, pituitary disease and basophilic adenoma, we found (table 9) that the hematocrit values were within normal range, but that the total circulating blood volume was markedly below normal, although it would probably rise to normal in the case of obese patients if the weight of the patient were ideal. In the obese patients the increased plasma volume closely followed the increase in body surface, but lagged far behind the increase in body weight. The fact that the blood volume lagged behind the plasma volume compared with the increased body weight and surface area, suggests that cell volume by hematocrit readings is less in obese than in normal patients.

**Avitaminosis (Scurvy)** We had an opportunity to study one case of scurvy, and to our surprise found a tremendous increase in plasma volume, to one and a half times normal (table 10), far more than in the cases of anemia and metabolic disturbances. The blood volume per kilogram of body weight was particularly increased, but the hematocrit values were below normal. The high plasma volume would indicate that the primary damage is not in the capillaries but in the plasma itself with a secondary disturbance in the capillaries corresponding to the condition that Eppinger<sup>21</sup> described as a primary plasma disturbance in certain cases of trauma.

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21 Eppinger, H. Die Blutreservoir des Menschen. *Innere Medizin, Klin Wchnschr* 12 5 (Jan 7) 1933.

TABLE 10—*Blood Volume in a Case of Arteriosclerosis (Scumy)*

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Ce for Each Kg of Ideal Body Weight	Cells by Hemato crit, per Cent	Blood Pressure, Mm of Hg Systolic	Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm
67	Rob	M	60.0	61.3	68	1.70	3,707	61.8	2,180	3,721	61.8	3,733	4.86	32.0	120	80	73		6

TABLE 11—*Blood Volumes in Cases of Neurocirculatory Asthenia*

Number	Name	Sex	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface, Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cc for Each Kg of Ideal Body Weight	Cells by Hemato crit, per Cent	Blood Pressure, Mm of Hg Systolic	Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure, Cm
68	Pfe	M	76.3	63.6	70	1.88	2,105	26.0	1,113	4,076	53.0	2,159	4.79	44.0	110	80	78	12	4
69	Gol	M	55.0	62.3	65	1.78	2,813	51.0	1,780	5,228	95.0	3,309	83.7	42.0	95	60	88	18	1
70	Gol	F	53.6	60.4	64	1.55	2,606	48.6	1,681	5,396	100.0	3,481	89.3	47.0	120	75	80	18	5
71	Gol	M	68.1	70.9	70	1.83	2,889	42.4	1,578	6,783	96.6	3,597	92.8	51.0	115	80	80	19	4
72	Wol	F	65.0	56.9	61	1.61	3,066	47.1	1,904	5,700	87.7	3,543	100.1	42.0	110	70	80	12	5
73	Smu	M	69.8	62.2	62	1.69	2,727	36.2	1,495	5,177	74.1	3,063	89.6	46.0	140	90	83	16	4
Average			64.9	62.7	64	1.69	2,667	41.8	1,791	5,360	84.4	3,192	86.6	45.3	115	75	82	15	4

TABLE 12—Average Values for the Various Groups, Showing Circulating Blood Volume, Venous Pressure, Blood Pressure and Circulation Times

Condition	Number Studied	Body Weight, Kg	Ideal Weight, Kg	Height, Inches	Body Surface Sq M	Total Plasma Volume, Cc	Cc for Each Kg of Body Weight	Total Blood Volume, Cc	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cc for Each Kg of Body Weight	Cc for Each Sq M of Body Surface	Cells by Hematocrit, per Cent	Blood Pressure, Mm of Hg Systolic      Diastolic	Pulse Rate	Circulatory Time (Cyanide), Seconds	Venous Pressure Cm
Normal	10	68.7	65.4	69	1.76	2,780	40.5	1,555	114.2	3,037	82.3	3,037	43.8	103      70	79	16	4
Hypert thyroidism	9	50.2	61.6	64	1.51	2,059	58.0	2,023	114.2	3,081	98.1	3,081	44.5	130      73	100	12	6
Cardiac disease (combined)	22	61.6	66.2	63	1.65	2,647	48.1	1,782	95.9	3,655	84.8	3,655	46.5	159      94	86	23	11
Plus form	7	58.9	64.0	62	1.58	2,988	51.8	1,961	115.9	4,479	109.2	4,479	50.0	171      105	90	21	19
Minus form	15	68.5	65.4	65	1.72	2,606	38.6	1,502	71.4	2,832	71.0	2,832	42.0	137      83	82	25	12
Hypertension (compensated)	5	61.0	62.5	62	1.60	2,786	44.0	1,618	81.6	3,020	77.6	3,020	42.4	190      103	90	13	7.7
Polycythæmia vera	7	57.9	65.9	61	1.57	2,475	42.2	1,571	167.7	6,090	145.7	6,090	67.5	140      84	78	18	4
Anæmia (varied)	6	63.1	58.6	61	1.60	3,123	49.8	1,937	74.9	2,938	81.0	2,938	30.0	124      74	84	13	8
Metabolic disorders	7	83.2	63.8	64	1.84	2,952	36.6	1,789	69.3	2,980	88.8	2,980	42.1	128      68	73	18	8
Avitaminosis (scurvy)	1	60.0	61.3	68	1.70	3,707	61.8	2,180	95.3	3,763	93.4	3,763	32.0	120      70	82		6
Neurocirculatory asthenia	6	64.9	62.7	64	1.60	2,667	41.8	1,791	84.4	3,192	86.6	3,192	45.5	115      75	82	15	1

**Neurocirculatory Asthenia** The six cases in this group were typical in their clinical manifestations. In some of the patients the condition simulated thyrotoxicosis (flushed skin, tachycardia, rapid pulse and increased basal metabolic rate), but both the plasma volume and the total circulating blood volume were within normal limits instead of attaining the high limits found in the patients with hyperthyroidism (table 11). The venous pressure and circulating time were normal. These observations definitely aided our clinical impression that these

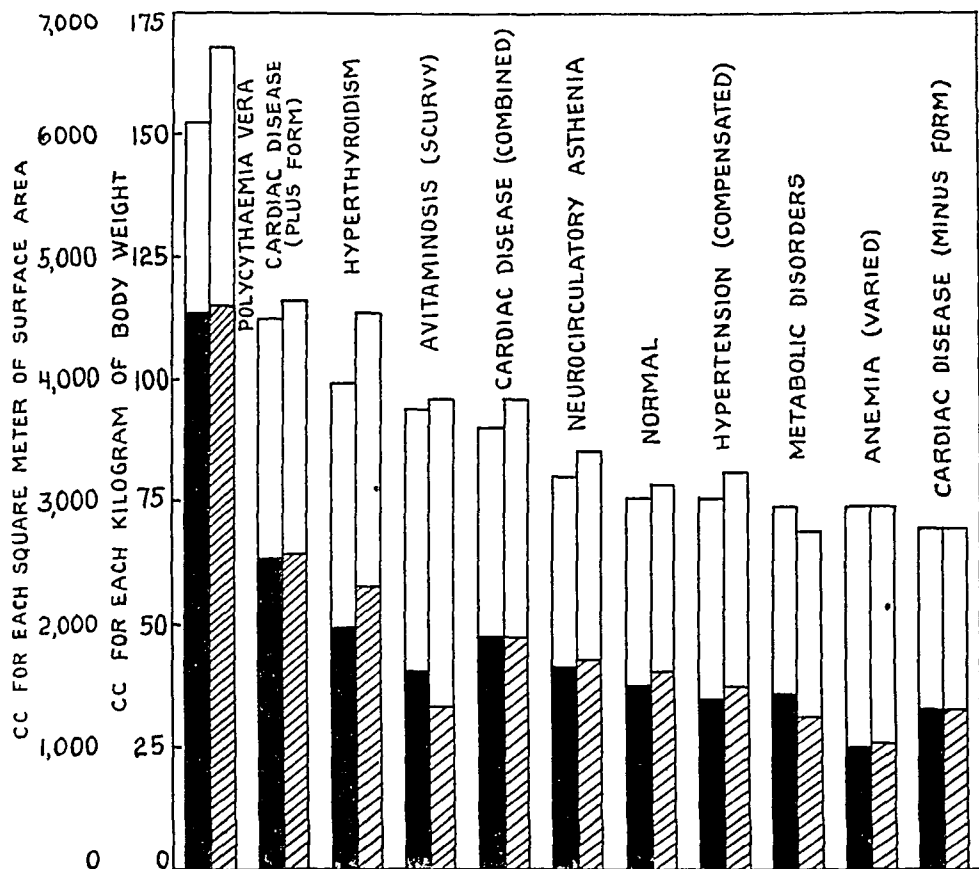


Fig 2—Circulating plasma volume and cell volume per square meter of body surface and kilogram of body weight in varied conditions. The solid columns indicate the plasma and cell volume for each square meter of surface area, and the cross-hatched columns the plasma and cell volume for each kilogram of body weight.

patients did not have thyrotoxicosis, but had borderline cases and a hyperthyroid constitution. The occurrence of a diminished blood volume at certain times in these cases would explain their orthostatic tachycardia and fatigue, headaches and dizziness. There was simultaneously a diminished cardiac output, with resultant poor nourishment of the tissues and skin.



## COMMENT

As the average of our determinations of blood volume in normal persons was fairly identical with the average findings in normal persons reported by other authors carrying out an identical technic under exactly the same conditions, we consider that there is definitely a standard normal value, ranging between 67 and 90 cc per kilogram of body weight, or an average of 78.4, and that the average normal circulating blood volume per square meter of body surface is 3,037 cc. There is less variation of body surface than of weight, hence the average circulating blood volume on the basis of body surface is a more exact average than the average per kilogram of body weight (fig 2). However, the surface area of the patient is not estimated as a routine procedure, whereas weight is, so that circulating blood volume per kilogram of body weight is more often ascertained than blood volume per square meter of surface area.

Although our results showed a variation in the respective groups of patients studied, nevertheless the average for each group, as in normal persons, was fairly constant, particularly when averages of blood volume per square meter of surface area were estimated. It is understood that psychic and nervous influences can affect end-results, but this is not serious, as seen in the fact that although patients with hyperthyroidism and those with neurocirculatory asthenia are extremely nervous, the end-results in these cases were constant for each group. Clinically, the patient with neurocirculatory asthenia is a highly nervous person, yet his blood volume was less than normal, in contradistinction to the less nervous patient with hyperthyroidism who showed an increased blood volume. This is well demonstrated in a case reported not long ago,<sup>22</sup> in which cardiodynamic determinations served as a differential factor between neurocirculatory asthenia and hyperthyroidism. In the present series, the average blood volume per kilogram of body weight in hyperthyroidism was 114.2 cc and in neurocirculatory asthenia, 84.4 cc.

Normally, there is a correlation between blood volume and minute volume, with a normal circulatory time. When there is no correlation, disturbance manifests itself in either a plus or minus form of decompensation, the plus form meaning increased and the minus form decreased circulating blood volume.

The clinical symptoms and signs in cases with a plus form of decompensation consist of orthopnea, dyspnea, restlessness, cyanosis of the bony projections, marked distention of the jugular veins,

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22 Goldbloom, A. A. Diagnostic Importance of Blood Volume and Cardiac Output Studies in a Borderline Case of Thyrotoxicosis, *M. Clin. North America* 17:279 (July) 1933.

enlarged liver and edema. In our group we found such conditions as decompensated essential hypertension, decompensated coronary disease with or without auricular fibrillation, decompensated arteriosclerotic valvular (aortic or mitral) disease and cor pulmonum. The etiologic factor was usually overstrain or arrhythmia.

In the cases with the minus form of decompensation the predominant symptoms and signs were fatigue, sleepiness, absence of dyspnea in the prone position, poorly filled jugular veins (filling not increased by pressure on the liver) and generally cyanosis. In this group we found such conditions as acute rheumatic fever, recurrent rheumatic endocarditis, auricular fibrillation (rheumatic), acute coronary occlusion, compensated hypertension with or without heart block and jaundice. The etiologic factors were recurrent infection, with their effects.

The differentiation of cardiovascular conditions into the plus or minus form of decompensation as based on the physiologic facts is of interest from the therapeutic standpoint. Certain drugs (caffeine, camphor, epinephrine and extract of the posterior lobe of the pituitary gland) tend to increase the blood volume, while others (histamine, digitalis, morphine and peptone) cause a decrease. The plus form of decompensation is caused by the failure of the peripheral circulation to carry adequate oxygen to the tissues, causing anoxemia, which stimulates the bone marrow and produces an excess of red blood cells. This is one explanation of why in the majority of cases showing the plus form of decompensation we found symptomatic polycythemia. The minus form of decompensation is caused, in the majority of cases, by an infectious factor which has an effect on the system similar to that of peptone, which diminishes the blood volume. An additional causative factor would seem to be an increase in the amount of blood hoarded in the various blood depots, because autopsy in these cases often reveals enlargement and congestion of the blood-hoarding organs. We found that in acute coronary occlusion with collapse caffeine and epinephrine are valuable, whereas in chronic coronary conditions these drugs are contraindicated.

We feel that the number of cases is too small for us to be dogmatic in our opinion and that further clinical studies are indicated. We have used the physiologic facts as a guide to therapy. In the minus forms of decompensation we have used drugs tending to increase the blood volume, as mentioned previously, while in the plus forms such drugs as digitalis and morphine have been of service. We do not wish to imply that in the minus form of decompensation digitalis is always contraindicated or that in the plus form digitalis is always indicated. It will require much more experience and evaluation of all the other factors before a definite stand can be taken on the question.

It is important to differentiate between the case showing the minus form of decompensation and one of shock or collapse. Although it is believed by some that the minus form of decompensation is actually a manifestation of collapse, our studies have shown that this is not true and that there are several points which differentiate the two conditions.

The outstanding observation in cases of polycythaemia vera was that the blood volume was increased to more than two and a half times normal, in fact, these showed the highest circulating volume of all the cases in our series, the second highest being the group with the plus form of decompensation. This high determination of blood volume is due to the increased hematocrit value in association with a normal or subnormal plasma volume. The high hematocrit value is a means of differentiating polycythaemia vera from polycythaemia symptomtica.

The case of scurvy was unusually interesting in that it gave the highest plasma volume in the series, and yet the total circulating blood volume was normal, owing to the low hematocrit value. Our impression is that the excessive plasma volume represents a primary disturbance in the plasma and that the capillary disturbance is secondary.

The conditions that showed an increase in blood volume in this series were the following: hyperthyroidism, hypertension with auricular fibrillation, complete heart block, disease of the coronary artery, arteriosclerotic valvular disease (mitral or aortic), chronic emphysema and bronchitis with decompensation and polycythaemia vera.

The conditions that showed a decreased blood volume were: acute rheumatic fever, recurrent rheumatic endocarditis, rheumatic valvular lesions (mitral), compensated hypertension, anemia (leukemia, secondary anemia and pernicious anemia), metabolic disturbances (obesity, basophilic adenoma and myxedema), neurocirculatory asthenia and avitaminosis (scurvy).

#### SUMMARY

Experimental work has shown that there are various blood depots, such as the spleen, liver, subpapillary plexus of the skin, large veins and lungs. Hence, there are two forms of blood volume: active circulating blood volume and passive hoarded blood volume. Clinically, the term blood volume refers to active circulating blood volume. A detailed description of the method and technic employed to determine the blood volume in seventy-three cases and the results are presented.

#### CONCLUSIONS

Although present clinical methods of determination of the blood volume may not be fool-proof, nevertheless our results, with the colloidal dye method described, have substantiated the belief that determination of the blood volume is not only of clinical value, but should be more widely utilized than at present.

Our observations show that hypertension in itself, does not increase blood volume. Therefore, in cases of thyrotoxicosis with hypertension, it is not the hypertension that is the cause of the increased blood volume. We have ascertained, also, that there is no relationship between increased basal metabolic rate and increased blood volume.

Cases of chronic cardiovascular disease fall, by determination of the blood volume, into two groups, the plus and minus forms of decompensation, the former indicating increased and the latter decreased blood volume. This division is important, not only therapeutically, but because when there is a change from a plus to a minus form of decompensation the existence of an acute coronary condition may be suspected. A minus form of decompensation is not identical with decreased blood volume due to shock or collapse, as there are clinical factors to differentiate them.

The determination of the blood volume is particularly helpful in the differential diagnosis of hyperthyroidism and neurocirculatory asthenia, and of polycythaemia vera and symptomatic polycythemia.

# Progress in Internal Medicine

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## BRIGHT'S DISEASE A REVIEW OF RECENT LITERATURE

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While this review of the subject of nephritis is intended primarily to summarize the most recent developments in that field, it is impossible to do so without going back into the literature of the past twenty years to trace the outlines of the growth of the present concepts and to give orientation to the discussion. I wish to state frankly at the outset that I have made no attempt to give a complete bibliography, even of the literature of the past year. Keeping in mind the desirability of clarity and the necessary limitation of space, I have sought to digest the great mass of literature and to quote key articles from which a more detailed bibliography can be obtained.

The modern trend of thought about Bright's disease began to crystallize twenty years ago with the publication of "Die Brightsche Nierenkrankheit," by Volhard and Fahr,<sup>1</sup> who introduced an anatomic and pathogenic classification of Bright's disease consisting of three main types, glomerulonephritis, nephrosis and nephrosclerosis. Following this Addis<sup>2</sup> adopted a clinical classification correlated with quantitative studies of the formed elements in the urinary sediment and with the renal lesions. The nomenclature of Addis may be readily translated into that of Volhard and Fahr. The hemorrhagic type of Bright's disease, or glomerulonephritis, is characterized by hematuria, acute, chronic or intermittent. The diffuse forms tend to be associated with hypertension (not regularly) and with nitrogen retention and inflammatory glomerular lesions. The degenerative forms of Bright's disease, or the nephroses, are characterized in the main by edema and proteinuria without hypertension or hematuria and by degenerative changes confined within the

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1 Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

2 Addis, Thomas. A Clinical Classification of Bright's Disease, *J. A. M. A.* 85:163 (July 18) 1925.

kidney to epithelial structures. The arteriosclerotic forms of Bright's disease, or the nephroscleroses, are characterized clinically by a marked hypertension preceding serious renal signs and histologically by arteriolar sclerosis.

A third great step forward came with the work of Van Slyke and his collaborators,<sup>3</sup> who published a monograph in 1930 in which the nosography of Bright's disease was enriched by the addition to the clinical picture of chemical and physiologic studies incident to observations on the courses of the different types of the disease. Van Slyke and his co-workers employed the classification of Addis, his method of enumerating the formed elements in the urinary sediment, all the modern resources for the chemical examination of the blood with particular reference to the proteins of the blood and urine, and the urea clearance test which was developed in Van Slyke's laboratory for the measurement of renal function. The resultant changes in renal anatomy which they were able to observe became doubly significant in view of the careful clinical and functional studies preceding them. This monograph stands as a masterpiece, one of the best examples of modern clinical investigation in which clinical, physiologic and morphologic methods are perfectly welded.

Minor readjustments have become necessary in the modern classification of Bright's disease as outlined in the preceding paragraphs. Some of these readjustments will be discussed subsequently. The most complete treatment of the entire subject available in English is found in the work of Fishberg.<sup>4</sup> A review by Fahr<sup>5</sup> covers the recent German literature only.

In most of the progressive American clinics the urinary sediment count (Addis) has become a procedure almost as firmly fixed as the blood cell counts. Hines<sup>6</sup> has recently devised a nomograph which greatly simplifies the computations and at the same time gives indications as to the magnitude of the errors involved.

Most of the achievements of modern medicine have depended on knowledge of the causes of disease and on ability to deal with them so as to achieve prevention or cure. The importance of a simple accurate classification of renal disease lies in the fact that such a classification is an

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3 Van Slyke, D. D., Stillman, E., Møller, E., Erich, W., McIntosh, J. F., Leiter, L., McKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, C. *Observations on the Courses of the Different Types of Bright's Disease and on the Resultant Changes in Renal Anatomy*, *Medicine* **9** 257, 1930.

4 Fishberg, A. M. *Hypertension and Nephritis*, ed. 3, Philadelphia, Lea & Febiger, 1934.

5 Fahr, T. *Beiträge zur Frage des Morbus Brightii*, *Klin. Wchnschr.* **13** 45, 1934.

6 Hines, D. C. *A Nomograph for Simplifying Computation of the Urine Sediment Count (Addis)*, *Am. J. M. Sc.* **187** 841, 1934.

essential step in the process of relating specific causes to specific effects. In studying the pathologic conditions in the kidneys the importance of careful cytologic differentiations is becoming increasingly appreciated particularly in regard to a comparison of lesions produced experimentally in animals with those observed post mortem in human beings. Two papers by McGregor<sup>7</sup> deal with the application of these methods to the study of the finer histology of the normal glomerulus and of the cytologic changes occurring in clinical glomerulonephritis. In the second article she traced the processes of endothelial proliferation, hyaline fiber formation and extracapillary changes through various stages up to the point of glomerular obliteration. Absence of exact morphologic criteria lies at the bottom of most of the differences of opinion which exist among various investigators who have endeavored to produce diffuse glomerulonephritis experimentally. The difficulty is well illustrated in a recent report by Rieder and Balzer.<sup>8</sup> After a critical review of all the experimental attempts to produce diffuse glomerulonephritis including their own experiments, these authors concluded that so far no one has produced with certainty anything more than focal nephritis. They admitted the close resemblance to glomerulonephritis of the lesions produced by the American investigators Duval and Hibberd, who injected a Berkefeld-filtered lysate of the peritoneal exudate of rabbits which had been inoculated intraperitoneally with scarlatinal streptococci after having been previously immunized against them.

#### GLOMERULONEPHRITIS AND RHEUMATIC FEVER

The opinion is widespread among students of Bright's disease that there is some relationship between hemorrhagic nephritis and streptococcic infection. In rheumatic fever a somewhat similar relationship is suspected though in neither disease has the exact nature of the relationship been made clear. For this reason recent investigations into the incidence of glomerulonephritis in rheumatic fever arouse considerable interest and are of theoretical importance. Using the urinary sediment count, Goldring and Wykoff<sup>9</sup> found that the excretion of formed elements and of protein occurred in excess of normal in a series of sixteen cases of acute rheumatic fever. The abnormal excretion rate continued for from four

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7 McGregor, L. The Finer Histology of the Normal Glomerulus, *Am J Path* **5** 545, 1929, Cytological Changes Occurring in the Glomerulus in Clinical Glomerulonephritis, *ibid* **5** 559, 1929.

8 Rieder, W., and Balzer, E. Ueber Versuche zur Erzeugung einer akuten diffusen Glomerulonephritis, *Ztschr f d ges exper Med* **92** 517, 1934.

9 Goldring, W., and Wykoff, J. Studies of the Kidney in Acute Infection. I. Observations with the Urine Sediment Count (Addis) in Acute Rheumatic Infection, *J Clin Investigation* **8** 569, 1930.

to ten weeks after the subsidence of the acute attack. A direct relationship was noted between the height of the fever and the quantitative abnormalities of the urine. No mention was made of the possible relationship of the urinary abnormalities to the antirheumatic remedies employed.

In a discussion of the glomerular lesions associated with endocarditis Bell<sup>10</sup> found evidence of diffuse glomerulitis in 22 per cent of a considerable series of cases of rheumatic endocarditis. The lesions are described as follows:

Nearly all the glomeruli are involved. There is a definite increase in the number of endothelial cells and their cytoplasm has become conspicuous. The capillary basement membrane is occasionally thickened. Occasionally there is also a notable increase in the number of leucocytes in the glomerular capillaries.

The changes were less pronounced than in the usual clinical cases, though in two instances the endothelial proliferation was quite prominent. Embolic lesions of the glomeruli were also noted in a small number of cases.

Baehr,<sup>11</sup> on the other hand, commented on the extreme rarity of glomerulonephritis in true rheumatic endocarditis, regarding it as an accidental complication and not a characteristic of the disease. He<sup>12</sup> expressed the belief that the intercurrent appearance of nephritis or a nephritic syndrome in a case which has been regarded as one of rheumatic endocarditis justifies doubt as to the accuracy of the diagnosis. Such a condition is much more likely to be subacute bacterial endocarditis in the bacteria-free stage, in which the incidence of glomerulonephritis is 33 per cent, the so-called atypical verrucous endocarditis of Libman or a renal manifestation of periarteritis nodosa.

It is not yet clear why two such careful workers as Bell and Baehr arrived at such different conclusions. It may be that there are geographic differences in the severity and type of rheumatic lesions, local differences in management of the cases or differences in the criteria used in the histologic diagnosis of the renal lesions. One must also assume that clinical opinions may differ somewhat about the differential diagnosis of simple rheumatic endocarditis, the bacteria-free stage of subacute bacterial endocarditis and the other atypical endocarditides mentioned by Baehr.

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10 Bell, E. T. Glomerular Lesions Associated with Endocarditis, *Am. J. Path.* **8** 639, 1932.

11 Baehr, G. Renal Complications of Endocarditis, *Tr. A. Am. Physicians* **46** 87, 1931.

12 Baehr, G., and Schiffman, A. The Rarity of Glomerulo-Nephritis in Rheumatic Fever and Its Significance, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman*, New York, International Press, 1932, vol. 1, p. 125.



In a very recent report Blaisdell<sup>13</sup> described the renal lesions found at autopsy in sixteen cases of rheumatic fever. A nonsuppurative periarteritis affecting the smaller arteries and arterioles was found in eight cases, perivascular scarring in four cases and a recurrent type of inflammation in two cases. Blaisdell did not observe the typical rheumatic arteritis of Pappenheimer and von Glahn in any of his cases. The arterial lesions bore a close resemblance to the perivascular lesions seen in the myocardium in rheumatic fever. Glomerular lesions were found in one case only, in close association with the arterial lesions and believed to be dependent on them.

#### NEPHRITIS AND THE TOXEMIAS OF PREGNANCY

The time has come when it is possible to study the renal diseases in pregnancy by the same methods as those used for renal disease in nonpregnant persons. Much of the confusion which has surrounded the subject in the past will disappear when modern methods of detecting renal disease are used at the onset of pregnancy and when the renal sequelae of the toxemias of pregnancy are followed up by such methods. Ambiguous and useless terms such as "low reserve kidney" will be discarded. Latent glomerulonephritis antedating pregnancy will be more frequently detected. In such cases some of the acute renal phenomena occurring later in pregnancy will be better understood, and they may be more frequently avoided.

Addis has classified the renal lesions of the toxemias of pregnancy under the heading of the degenerative type of Bright's disease, in spite of the concomitant hypertension and vascular lesions. The importance of the latter factors cannot be overlooked, however, and there is increasing evidence that the renal lesions of pregnancy should be grouped with the nephroscleroses rather than with the nephroses.

Bell<sup>14</sup> described the renal lesions of eclampsia and pre-eclampsia. He found a characteristic glomerular lesion in which the lumens of the capillaries are narrowed by a thickening of the basement membrane and sometimes by a slight or moderate endothelial proliferation. He stated that the thickening of the capillary basement membrane is characteristic of the kidneys in all forms of hypertension. In all of his patients in whom eclamptic phenomena were noted in nephritis preceding pregnancy autopsies revealed the presence of the characteristic lesions of diffuse glomerular nephritis. In one case lesions resulting from eclampsia which occurred seven years previously were described. They consisted of focal

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13 Blaisdell, J. L. The Renal Lesions of Rheumatic Fever, *Am J Path* 10 287, 1934

14 Bell, E. T. Renal Lesions in the Toxemias of Pregnancy, *Am J Path* 8 1, 1932

hyaline areas in the glomeruli with partial or complete glomerular obliteration and varying degrees of tubular atrophy, together with the fresh lesions of the second attack of eclampsia which caused death. Regarding the pathogenesis Bell was inclined to reject the Volhard theory of angiospastic ischemia in spite of the fact that glomerular ischemia was a regular finding and that symmetrical cortical necrosis sometimes occurs. Bell favored the theory of a circulating toxin. The glomerular lesions of eclampsia were described originally by Loehlein. They are also described by Baird and Dunn<sup>15</sup> who confirmed the observations of Bell.

Gibberd<sup>16</sup> called attention to the significance of recurrence of the late toxemias of pregnancy. Observations were made on an unselected group of previously normal women in whom late toxemias of pregnancy developed, the criterion of which was the occurrence of renal albuminuria not associated with pyelitis or infection. It was found that a first toxemia may affect a previously healthy woman in one of three ways. It may immediately give rise to a chronic nephritis, it may be followed by more or less habitual recurrence in subsequent pregnancies, the kidneys being apparently normal and the patient healthy in the intervening periods, or it may leave the patient entirely normal. To explain the second group Gibberd proposed the theory of an "occult nephritis." It accords well with the clinical facts, but it lacks anatomic support, unless one considers the case of Bell in which healed lesions resulting from a previous eclampsia were noted. Gibberd advocated the early induction of labor in the first toxemia in order to diminish the definite risk of a chronic nephritis (which occurs in from 10 to 15 per cent of patients) and the greater risk of an occult nephritis (reported in from 40 to 50 per cent).

#### DEGENERATIVE FORMS OF BRIGHT'S DISEASE—THE NEPHROSES

It has been assumed by most recent workers that a true genuine or "lipoid" nephrosis exists, in spite of the fact that the nephrotic stage of glomerulonephritis presents an almost identical syndrome of common occurrence. The true lipoid nephrosis, if it exists at all, appears to be exceedingly rare. Patients presenting this syndrome have been studied at autopsy by competent observers with the occasional finding of a case in which inflammatory glomerular lesions were absent. Fahr and others have described degenerative lesions of the glomeruli in a few of these patients and have even described a type of contracted kidney which they consider to be secondary to degenerative lesions of the glomeruli.

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15 Baird, D., and Dunn, J. S. Renal Lesions in Eclampsia and Nephritis of Pregnancy, *J. Path. & Bact.* **37** 291, 1933.

16 Gibberd, G. F. The Significance of Recurrence of the Late Toxemias of Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **41** 23, 1934.

Bell<sup>17</sup> studied, post mortem, the kidneys of ten patients who were assumed to have had lipoid nephrosis. All ten were considered by Bell to have a form of glomerulonephritis in which the glomeruli were damaged without sufficient obstruction of the capillaries to interfere with glomerular function or to cause tubular atrophy.

While such observations on ten patients do not exclude the possibility that a true lipoid nephrosis exists, they indicate the need of extreme caution in making that diagnosis unless the entire clinical course of the disease has been subjected to intensive scrutiny with particular reference to the presence of blood in the urine.

Concerning renal amyloidosis, Dixon<sup>18</sup> collected one hundred cases from 9,813 consecutive autopsies. Tuberculosis had been the etiologic factor in 78 per cent of the cases, malignant tumors in 9 per cent, intrathoracic suppuration in 7 per cent and chronic osteomyelitis in 1 per cent. Amyloid deposits in the glomeruli accounted for the renal insufficiency, but deposits in the smaller arteries were also regarded as playing a rôle. It was found that amyloid deposits occasionally occurred in other types of chronic nephritis.

#### NEPHROSES DUE TO HEAVY METALS

Bernard and Rossier<sup>19</sup> have described in considerable detail the renal and urinary abnormalities which may develop in a small percentage of cases of tuberculosis in the course of treatment with salts of gold. The most common phenomenon is a transient albuminuria. Sometimes the symptoms of azotemia and oliguria are noted. In severe forms lumbar pain, anuria, massive albuminuria, edema, hematuria and uremic symptoms are observed. Death may occur, but recovery generally ensues if the patient does not succumb in the acute stages. In general, the severity of the phenomena observed is proportional to the size of the dose administered. Cases are on record in which there were cumulative insults to the kidneys resulting from an injudicious repetition of doses before the effects of previous doses had disappeared. In other cases there was much evidence to suggest hypersusceptibility to injury by gold preparations analogous to the marked intolerance sometimes exhibited toward arsenic, in that severe renal damage followed the administration of relatively small doses. Bernard and Rossier discussed the factors which may enter into the production of the renal lesions. While it is probable that gold preparations alone account for the majority of cases, some other toxic factor must be postulated in order to account for those in

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17 Bell, E. T. Lipoid Nephrosis, *Am J Path* 5: 587, 1929.

18 Dixon, H. M. Renal Amyloidosis in Relation to Renal Insufficiency, *Am J M Sc* 187: 401, 1934.

19 Bernard, E., and Rossier, A. Sur la nephrite par les sels d'or, *Paris med* 1: 28, 1934.

which acute nephritis occurs. This additional factor may have something to do with the reaction in tuberculosis which follows the use of gold salts. Mention is made of the observations of other workers which suggest that gold salts occasionally hasten or cause the rapid development of amyloidosis.

Vallery-Radot, Gilbrin and Gauthier-Villars<sup>20</sup> described the renal lesions produced experimentally in animals by injection of large doses of gold salts. Black casts were found in the convoluted tubules after repeated injections, varying in number according to the amount of gold preparation given. No renal lesions were observed except those in the convoluted tubules. Glomerular lesions and desquamative changes in the collecting tubules were never found.

One of the most important contributions in the past year is the announcement by Rosenthal<sup>21</sup> of an effective antidote for acute mercury poisoning. This antidote is sodium formaldehyde sulfoxylate, a powerful reducing agent by means of which the toxic mercury compounds are reduced to the mercurous state or to metallic mercury. The procedure recommended by Rosenthal is quoted in detail as follows:

Gastric lavage is done through a stomach tube with a 5 per cent solution of sulfoxylate, approximately 200 cc of this solution being left in the stomach. Immediately following this, 10 Gm dissolved in from 100 to 200 cc of distilled water is slowly injected intravenously, from twenty to thirty minutes being permitted for the injection. From four to six hours after the completion of this injection the intravenous administration of from 5 to 10 Gm of sulfoxylate may be repeated in severe cases. If it is feasible to test the blood serum against corrosive mercuric chloride, the time that this reaction becomes faintly positive or negative (from three to five hours) may be taken as an indication of the time to give this second intravenous dose of sulfoxylate. If colitis later develops, I employ high colonic irrigations with a 1:1,000 solution of sulfoxylate once or twice daily.

Such treatment is said to be highly effective even when given as late as an hour and a half after the ingestion of the mercury.

#### ARTERIOSCLEROTIC FORMS OF BRIGHT'S DISEASE—THE NEPHROSCLEROSES

Of cases in which pronounced hypertension precedes serious renal signs many clinicians recognize a benign and a malignant type. In the benign type nephrosclerosis rarely advances to renal insufficiency. The malignant form of nephrosclerosis progresses rapidly to the uremic

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20 Vallery-Radot, P., Gilbrin, E., and Gauthier-Villars, P. Mode d'élimination du métal dans les néphrites expérimentales par les sels d'or, *Presse med* **41** 1827, 1933.

21 Rosenthal, S. M. Mercury Poisoning, *J. A. M. A.* **102** 1273 (April 21) 1934.

stage Hematuria is not characteristic of the benign type, but it commonly occurs in the malignant form of nephrosclerosis, a fact which creates some confusion in interpretation and a difficulty in differential diagnosis between glomerulonephritis and malignant nephrosclerosis

An interesting and important study of a patient with malignant hypertension and nephrosclerosis has been made by Weiss, Parker and Robb<sup>22</sup> Their patient had hematuria arising from the left kidney, of such severity that this kidney was removed At the operation, performed under spinal anesthesia, functional tests were carried out, and the oxygen content of blood from the renal artery and renal vein was determined Control observations of a similar character were made on three subjects in whom the kidneys were normal and on whom operations for the suspension of a mobile kidney were performed under spinal anesthesia

The difference in the oxygen content between the arterial and the venous blood in normal kidneys was about 2.4 per cent, and the amount of oxygen utilized by the kidneys was 13 per cent of the average oxygen content of the arterial blood In the patient with malignant hypertension the oxygen content of the venous blood was actually higher than that of the arterial blood, owing to the increased concentration due to loss of water The results indicated that there was an excessively rapid flow of blood through the glomerular and tubular capillaries under the force of an elevated arterial pressure The authors inferred that there is a high intratubular pressure as well as a rapid flow of the filtrate through the tubules, which accounts for the dilatation of these structures observed histologically Microscopic examination showed glomeruli with a characteristic thickening of capillary basement membranes and in various stages of hyalinization During the interval of sixty-seven days which elapsed between the nephrectomy and the examination of the right kidney at autopsy there occurred a great increase in the proportion of glomeruli with thickened basement membranes and of those with complete sclerosis The hematuria was believed to have resulted from the rupture of glomerular and tubular capillaries under the stress of a greatly increased capillary pressure

Another study of the histologic changes observed in the kidneys in malignant hypertension is that of Cain,<sup>23</sup> who reviewed the literature on the subject In his study the major emphasis is laid on the arteriolar changes

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22 Weiss, S., Parker, F., Jr., and Robb, G. P. A Correlation of Hemodynamics, Function and Histological Structure of the Kidney of Malignant Arterial Hypertension with Malignant Nephrosclerosis, *Ann Int Med* 6: 1599, 1933

23 Cain, E. F. Malignant Hypertension. The Histologic Changes in the Kidneys, *Arch Int Med* 53: 832 (June) 1934

In considering the etiology of the nephroscleroses one must consider that of the hypertension on which they depend. A review of the literature is beyond the limited scope of this article. One etiologic factor is worthy of more than cursory discussion, however.

Certain agencies have recently called attention to the widespread dissemination of lead in foods as a result of the spraying of fruits and vegetables and of other processes of metallic contamination. This knowledge has resulted in a great renewal of interest in the toxic properties of lead. From Queensland has come a report by Fairly<sup>24</sup> of a governmental inquiry as to the importance of lead as a causative factor in chronic nephritis, which condition was found to be three times as common in people under 40 years of age in Queensland as in other Australian states. Typical lead poisoning occurs more commonly in the children of Queensland. Investigation showed that a large proportion of the children with lead poisoning died of chronic nephritis before the age of 40. The report describes the manner in which the children acquire lead from weathered lead paint on verandas to which they are often confined. Regulations are recommended which would prohibit the use of lead in paints on toys, furniture, pencils and verandas. It is also urged that stringent limitations be put on the use of lead arsenate for the spraying of fruits and vegetables. In the analyses it was found "Of 31 samples of cabbage, 29 showed from 3 to 20 grains [from 0.195 to 1.30 Gm.] of lead arsenate per cabbage."

#### TESTS OF RENAL FUNCTION

Two methods of testing the functional capacity of the kidneys have been gaining steadily in vogue. These are the urea clearance test of Møller, McIntosh and Van Slyke<sup>25</sup> and the creatinine clearance test of Holten and Rehberg<sup>26</sup>. The significance and relative accuracy of these tests have been studied by several workers. Hayman and Johnson<sup>27</sup> carried out experiments to determine the relation of the results of these two tests to the number of glomeruli found in the human kidney at

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24 Fairley, K. D. A Review of the Evidence Relating to Lead as an Aetiological Agent in Chronic Nephritis in Queensland, *M. J. Australia* **1** 600, 1934.

25 Møller, E., McIntosh, J. F., and Van Slyke, D. D. Relationship Between Urine Volume and Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6** 427, 1928, Relationship Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease, *ibid.* **6** 485, 1928.

26 Holten, C., and Rehberg, P. B. Studies on the Pathological Function of the Kidneys in Renal Disease, Especially Bright's Disease, *Acta med. Scandinav.* **74** 479 and 538, 1931.

27 Hayman, J. M., Jr., and Johnson, J. M. Experiments on the Relation of Creatinine and Urea Clearance Tests of Kidney Function and the Number of Glomeruli in the Human Kidney Obtained at Autopsy, *J. Clin. Investigation* **12** 877, 1933.

autopsy They employed Kunkel's modification of Vimtrup's method in which glomeruli were counted in a suspension of digested kidney after injection at constant pressure of potassium ferrocyanide and ferric ammonium citrate and digestion with hydrochloric acid Counts of injected and uninjected glomeruli were also made in blocks of kidney after embedding and sectioning In the kidneys of twelve persons without any evidence of renal disease the counts for one kidney ranged from 800,000 to 1,530,000, the mean was 1,156,000 and the standard deviation 191,266 The results of creatinine and urea clearance tests were compared with the number of glomeruli found in a series of patients on whom the tests were performed shortly before death In both glomerulonephritis and the arteriosclerotic form of Bright's disease the reduction in the clearance as shown by the tests was associated with a reduction in the number of injected glomeruli In pneumonia and pyelonephritis the clearance may be reduced in the presence of a normal number of glomeruli It is suggested that this is due to the back diffusion of the test substances through damaged tubular cells These facts suggest that the clearance tests may be taken as the measure of the amount of functioning renal tissue only in the absence of toxic factors producing damage to the tubular cells

Hayman, Halsted and Seyler<sup>28</sup> made a comparison of the creatinine and the urea clearance both in normal persons and in those with Bright's disease The variability of the two tests from the mean normal was approximately the same but was of considerable magnitude For the maximum urea clearance the range was from 38 to 112 cc per minute with an average of about 75 cc The mean standard urea clearance was 51 cc, with a range from 30 to 67 cc and a standard deviation of 10.11 cc In regard to the creatinine clearance test Hayman, Halsted and Seyler pointed out that results must be as low as 60 cc per minute to be considered definitely abnormal although the mean creatinine clearance in one hundred and thirty observations on fifty-nine normal subjects was 148 cc per minute A creatinine clearance of from 60 to 80 cc per minute is doubtfully normal but indicates an abnormal condition if a repetition of the test gives results in the same range

The creatinine clearance test is based on studies made by Rehberg which led him to believe that creatinine is not resorbed by the tubules and that it can be used, therefore, to study the rate of glomerular filtration Hayman and his co-workers expressed the belief that their observations cast doubt on the nonresorbability of creatinine and indicate that it does not measure glomerular filtration under all conditions While this would invalidate the conclusions of some experiments based on

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28 Hayman, J. M., Jr., Halsted, J. A., and Seyler, L. E. A Comparison of the Creatinine and Urea Clearance Test of Kidney Function, *J. Clin. Investigation* 12: 861, 1933

Rehberg's assumptions, it would not necessarily destroy the value of the creatinine clearance test as a clinical test of renal function

Lassen and Husfeldt<sup>29</sup> took advantage of the opportunity of studying the creatinine clearance in young men with a normal heart and normal kidneys before, during and after the marked change in blood pressure occurring under spinal anesthesia. At the height of the anesthesia, when the fall in blood pressure was most marked, they found a great decrease in glomerular filtration as calculated from the creatinine, the decrease being proportional to the fall in blood pressure. At the same time the concentration index  $\frac{\text{Concentration of Creatinine in Urine}}{\text{Concentration of Creatinine in Blood}}$  increased significantly, indicating that the tubular function was normal as far as the resorption of water was concerned. The great decrease in the volume of urine which occurred during the fall in pressure was due partly to the great resorption of water and partly to the low volume of glomerular filtrate. They found that diuresis could be kept near normal if racemic ephedrine and caffeine were used to maintain the blood pressure at a higher level.

In contrast to the observations just cited, Page<sup>30</sup> found that fluctuations in blood pressure exercised little influence on the urea clearance. The fluctuations which he induced in hypertensive patients by sodium sulphocyanate or by colloidal sulphur did not impair the efficiency of urea clearance. The fluctuations observed were not comparable in extent to those observed by Lassen and Husfeldt,<sup>29</sup> and they affected the systolic blood pressure to a much greater extent than the diastolic.

Alving and Van Slyke<sup>31</sup> have investigated the significance of the widely used concentration and dilution tests. They found that concentration tests are sensitive for qualitative detection of damaged renal function but not suitable for measuring its extent. For instance, following acute nephritis the concentration test may show abnormal results for a long time after the urea clearance has returned to normal. In chronic nephritis the concentration may not decrease while the urea clearance falls to the uremic level. In general, it may be said that the urea clearance measures the function of excreting nitrogen and that the concentration test measures the function of excreting mineral salts. Alving and Van Slyke did not discover any useful information contributed by the dilution tests.

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29 Lassen, H. C. A., and Husfeldt, E. Kidney Function and Blood Pressure, *J. Clin. Investigation* **13** 263, 1934.

30 Page, I. L. The Effect on Renal Efficiency of Lowering the Blood Pressure in Cases of Essential Hypertension and Nephritis. *J. Clin. Investigation* **13** 909, 1934.

31 Alving, A. S., and Van Slyke, D. D. The Significance of Concentration and Dilution Tests in Bright's Disease, *J. Clin. Investigation* **13** 969, 1934.



## PATHOLOGIC PHYSIOLOGY OF BRIGHT'S DISEASE

The biochemical aspects of the great functional derangements of Bright's disease manifested in uremia, acidosis and edema have been dealt with in an encyclopedic way by Peters and Van Slyke<sup>32</sup> Since that time no observations of fundamental significance have been added to the knowledge of uremia and its almost invariable concomitant acidosis

In dealing with the subject of uremia it will materially assist the student to familiarize himself with the differentiation between "true" and "false" uremia which Volhard<sup>33</sup> has proposed The "false" uremic phenomena in the sense of Volhard are those which may be embodied under the concept of "hypertensive encephalopathy," namely, eclamptic seizures, transient focal neurologic disturbances, Cheyne-Stokes breathing, etc., all of which may be observed in hypertensive states in the absence of renal insufficiency The "true" uremia includes only the phenomena which result from the failure of renal function, namely, anorexia, nausea, vomiting, hyperpnea of the Kussmaul type, stupor, coma, the associated increases in the nonprotein nitrogenous constituents of the blood and the alterations in blood electrolytes Peters and Van Slyke<sup>32</sup> made it clear that the nitrogen retention is not the cause of these phenomena, though it is a good measure of their intensity In general, the theories of uremia which are based on the retention of a hypothetical toxin are inadequate to explain all the facts A far more satisfactory working concept of uremia results if one considers it as a breakdown of the normal regulatory functions of the kidneys in their contribution to the maintenance of the internal environment of the cells constantly in an optimal state In such a concept retention phenomena play a part, as evidenced by the retention of nonprotein nitrogen, inorganic acid radicals and aromatic oxacid Of equal importance are the failures of the kidney to retain and conserve essential substances, for instance, the failure to retain fixed bases which results from the breakdown of the ammonia-forming function of the kidneys In the abnormal states of equilibrium between inorganic and organic acids and bases and in the state of hydration of the body, failures both of retention and of excretion and compensatory readjustments of extrarenal mechanisms play a part

## EDEMA IN NEPHRITIS

The biochemical and biophysical phenomena of edema have also been exhaustively reviewed by Peters and Van Slyke<sup>32</sup> up to 1931 To

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<sup>32</sup> Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry Interpretations*, Baltimore, Williams & Wilkins Company, 1931

<sup>33</sup> Volhard, F. *Nieren und ableitende Harnwege*, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, ed 2, Berlin, Julius Springer, 1931, vol 6, pts 1 and 2

this field of study Peters has been one of the principal contributors. Many years ago Starling called attention to the importance of the osmotic pressure of the serum proteins in relation to the intracapillary pressure in maintaining the balance of water exchange through a capillary wall. From this as a starting point great advances have been made in the understanding of the pathologic physiology of edema.

Weech<sup>34</sup> has very recently given a clear, terse review of the known facts regarding the relationships of oncotic pressure, capillary pressure, capillary permeability, protein content of the lymph, lymph flow, elasticity of the tissues, mechanical pressure in tissue spaces, variations in salt intake and certain renal factors in diuresis. These are the best known of the variable factors which must be considered in an analysis of the mechanism of edema. Weech referred particularly to the more recent work of Drinker and Fields, of Landis and of Schade and Clausen, who have been important contributors to this field.

I have occasionally observed patients without edema in whom the values of the serum proteins and colloidal oncotic pressure were below those at which Moore and Van Slyke<sup>35</sup> commonly found edema to occur. Of particular interest in this connection are some comparisons made by Weech of values for lymph protein and serum protein in normal and in edematous dogs, which indicate that in some of the cases of edema with low serum proteins the capillary walls become less permeable than normal, since the ratio of serum protein to lymph protein was 4.4 in normal as compared with 16.1 in edematous animals. He also measured the relationship of the oncotic pressure of the serum to the rate of lymph flow. In a group of normal dogs an average oncotic pressure of 20.7 mm. of mercury was accompanied by an average lymph flow of 1.71 cc. in ten minutes, in edematous dogs with an average pressure of 9.1 mm. of mercury the lymph flow was 2.09 cc. in ten minutes. These findings suggest a partial answer to the question why abnormally low serum proteins are not always accompanied by edema. Kylin<sup>36</sup> suggested another factor which must not be overlooked. He observed a case of nephrosis in which the colloid oncotic pressure of the blood fell as low as from 100 to 150 mm. of water without any detectable edema. He called attention to the fact that Leiter<sup>37</sup> produced edema experimentally by the com-

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34 Weech, A. A. Fluid Distribution and Edema, *Bull. New York Acad. Med.* **10** 269, 1934.

35 Moore, N. S., and Van Slyke, D. D. The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* **8** 337, 1930.

36 Kylin, E. Zur Frage der Pathogenese des Nephroedems, *Acta med. Scandinav.* **80** 403, 1933.

37 Leiter, L. Experimental Nephrotic Edema, *Arch. Int. Med.* **48** 1 (July) 1931.

bined process of decreasing the plasma proteins (plasmapheresis) and giving the animals large quantities of salt. Kylin decreased the colloidal oncotic pressure of the blood of fifteen dogs to the level of from 50 to 100 mm of mercury. Salt was not given, and edema did not occur, from which facts Kylin concluded that the hydropigenous action of salt is essential to the production of edema by diminished colloidal oncotic pressure.

The special interests of the reviewer have centered on the factors concerned in the regeneration of the plasma proteins when these have become depleted by inanition or by excessive albuminuria. A brief outline of these factors has recently been presented<sup>38</sup>

The first workers who made an experimental attack on the problem of regeneration of serum proteins were Kerr, Hurwitz and Whipple,<sup>39</sup> who discovered that in normal conditions there were reserves of serum proteins, since these bodies were replaced during fasting after one or two depletions by plasmapheresis. They also found that regeneration was more rapid when the experimental animals were fed liver rather than beef or milk as a source of protein. That the liver plays an important rôle in this regeneration is shown by the delay in replacement of plasma proteins after injury of the liver or after the production of an Eck fistula.

It has long been known through the advocacy of Epstein that large amounts of protein in the diet exert a beneficial effect in the management of lipoid nephroses. Keutmann and McCann<sup>40</sup> in undertaking a study of regeneration of plasma protein in glomerulonephritis found it necessary to determine whether or not the use of diets high in protein had any adverse effects on the course of the disease. They were able to show only beneficial effects, since hematuria, quantitatively measured, was not increased and functional tests showed improvement. These studies have been continued for more than two years, but so far only a preliminary statement of the results has been given.<sup>38</sup> It has been found that protein may be readily stored in the body in glomerulonephritis when given in adequate amounts and subjected to the sparing action of a liberal supply of carbohydrate and fat. The difficulty encountered was that of increasing the amount of proteins in circulation in the plasma.

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38 McCann, W. S. *The Clinical Significance of the Plasma Proteins*, New York State J. Med. **34** 923, 1934.

39 Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. *Regeneration of Blood Serum Proteins. I. Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion*, *Am. J. Physiol.* **47** 356, 1918; *Regeneration of Blood Serum Proteins. II. Influence of Diet upon Curve of Protein Regeneration Following Plasma Depletion*, *ibid.* **37** 370, 1918.

40 Keutmann, E. H., and McCann, W. S. *Dietary Protein in Hemorrhagic Bright's Disease*, *J. Clin. Investigation* **9** 973, 1932.

In some cases the plasma proteins did not increase appreciably in spite of an enormous deposition of protein

Lepore<sup>41</sup> has shown that a close relation exists between the concentration of plasma protein and plasma volume. Whipple and his co-workers<sup>42</sup> have shown that the total amount of plasma protein decreases during starvation but that this decrease is masked by a simultaneous shrinkage in plasma volume, so that the percentage of protein is not much altered even when the total amount circulating is reduced to one-half the normal. It is known that the amount of plasma proteins cannot be increased above normal by means of high protein diets. Holman, Mahoney and Whipple<sup>43</sup> found that when the reserves of plasma proteins are depleted by plasmapheresis the regeneration of new plasma proteins can be controlled at will by dietary measures. Liver and casein and some vegetable proteins were found to be efficient in promoting regeneration. These authors found that before testing the efficiency of various foods the protein reserves of the test animals should first be exhausted. Globulin was found to be more easily regenerated than albumin, small amounts of it being produced even on their basal diet which contained only a little protein (from potato). A reversal of the albumin to globulin ratio occurred in some patients on the basal diet alone and in all patients with plasmapheresis on the basal diet. With a liver diet the production of albumin exceeded that of globulin.

The same investigators found that large amounts of blood plasma can be given intravenously to normal dogs over a period of several weeks without any significant loss of protein in the urine. Dogs could be kept in nitrogen equilibrium when they received sugar orally and plasma intravenously. When plasma was fed by mouth under identical conditions the urinary nitrogen was a little higher, a fact which suggests that injected protein is utilized more completely. Holman, Mahoney and Whipple concluded that "all these facts point to a *dynamic equilibrium* between tissue protein and plasma protein depending upon the physiological needs of the moment." Elsewhere<sup>44</sup> attention has been called to the analogy which may be drawn between the relation of glycogen to blood sugar and the plasma protein reservoir to amino-acids. Depletion of the plasma protein reservoir may be the result of inanition, of loss of protein in the urine or of any factors leading to a negative nitrogen balance. The reserve may be restored by adequate nutrition. Overfilling is probably prevented by the specific dynamic action of protein.

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41 Lepore, M. J. Relation of Plasma Volume to Plasma Protein Concentration, *Proc Soc Exper Biol & Med* **30** 268, 1932.

42 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Regeneration Controlled by Diet, *J Exper Med* **59** 251, 1934.

43 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Given by Vein Utilized in Body Metabolism *J Exper Med* **59** 269, 1934, footnote 42.

These facts have been extensively reviewed because of their obvious importance in the dietary management of Bright's disease, in particular of the nephrotic syndromes. As pointed out elsewhere,<sup>44</sup> protein which is being deposited makes no demand on the excretory function, so that it is possible in many cases to build up the nutritive condition of patients whose renal function has been reduced to the uremic stage, with the result that life and capacity to work have not infrequently been prolonged.

Until the specific causes of the various types of Bright's disease can be dealt with in prevention or cure, treatment must be largely dependent on skilful management of the nutritional requirements, particularly with regard to proteins, bases and hematopoietic substances, together with such adjustment of the water and chloride intake as the need for diuresis and tendency to edema may require.

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<sup>44</sup> McCann W S    The Many Sided Question of Protein in Nephritis, *Ann Int Med* 5 579, 1931

## Book Reviews

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**Periodic Fertility and Sterility in Woman** By Prof Dr H Knaus With a foreword by Prof F H A Marshall, FRS, Cambridge Authorized English translation by D H Kitchin and Kathleen Kitchin, M Sc, M B, B S, London Price, \$6, post-free, \$6.50 Pp 160, with 64 illustrations and 12 tables Vienna Wilhelm Maudrich, 1934

An ideal method of controlling conception, it has been said, must be harmless and convenient and must not offend taste or esthetic sensibilities, it should not affect sensation, it should be easily applied and it should be cheap and safe. The Ogino-Knaus method, it is claimed, fulfils all these requirements, with the possible exception of a certain amount of inconvenience. Periods of abstinence are required, but this is probably not a serious difficulty. Furthermore, the method has the approval of the church and the synagogue. Whether it is really safe is still a matter of discussion. The authors claim it to be so in 90 per cent of cases, as large a percentage of effectiveness as has been demonstrated for any of the mechanical and chemical devices available. The failures are attributed to very irregular menstruation, poor general health, disobedience and inadequate attention on the part of the women to keeping accurate records of their menstrual cycles.

On the other hand, critics of the method point out that conceptions are known to have taken place during the Ogino-Knaus "safe period," and that this alone throws doubt on the underlying theory, that more women menstruate irregularly than regularly, contrary to the contention of Knaus, and that the frequency with which a woman's rhythm may be upset by such trivial incidents as unusual physical exercise or change of climate, as is admitted by Knaus, makes the method unreliable. Hartman, whose work with monkeys supports the theory maintained by Knaus, stated "That the prevailing opinion that ovulation may occur at any time of the cycle cannot be brushed aside without much further proof, at least so far as the human species is concerned."

Whatever the outcome of this discussion, the "safe period" of Ogino and Knaus has aroused such general interest and has been so widely discussed in newspapers, periodicals and several popular books that the physician will welcome this exposition of the subject by Knaus, the present monograph representing the summation of all his previous papers on the subject.

The translation is exceptionally satisfactory. The biologic basis of conception is considered briefly but adequately, and the author's method of determining the date of ovulation in woman is discussed in detail. It depends on graphic records of the effect of injections of solution of pituitary on uterine tone, the reaction to pituitary being lost on the day when ovulation is predicted and secretion of the hormone of the corpus luteum begins. It is concluded that ovulation occurs on the fifteenth day before the onset of the next period, when the reproductive physiology is normal. The corpus luteum has an autonomous function regularly lasting fourteen days not only in the human being but also in many other species.

The need for precise recording of the dates of menstruation in determining the character of the cycle in the individual is discussed, and a menstrual calendar is described. "In the case of irregular cycles the ovulation date may be on any day in the period of time which falls between the two ovulation dates of the shortest and longest cycles respectively, the cycles being recorded for at least twelve months."

The final chapters are devoted to Ogino's contributions, a historical review of the idea of periodic fertility and the scientific evidence by which this method of the prevention of conception is supported.

**Amoebiasis and Amoebic Dysentery** By Charles F Craig Price, \$5  
Pp 315, with 54 illustrations Springfield, Ill Charles C Thomas, Publisher,  
1934

The recent rapid advances in the knowledge of amebiasis have left the average physician not only behind but in a state of confusion. The old concept of amoebic dysentery as a drastic disease confined more or less to the tropics has been shattered, and it is claimed that 10, 20 or even 50 per cent of healthy persons pass cysts of pathogenic amebas in the feces, and, what is even worse, actually have some disability as a result of the infestation. One was shocked to hear recently of a large outbreak of acute dysentery in one of our greatest cities, and there are reports on every hand of new drugs which are said to be better than the old standby emetine, and with most of which the general practitioner has had little chance to experiment.

The time is clearly ripe for an authoritative summary of the whole problem, and no pen is better qualified to write this than that of Colonel Craig, long a student in the field of amebiasis. Three hundred and five pages of text with many pictures of parasites and specimens of tissue, together with tables and charts, describe the history, epidemiology, pathology, clinical manifestations and treatment. The newer anti-amoebic drugs are discussed critically with reference to both acute dysentery and the carrier state, and each chapter is followed by a list of useful references.

With only one phase of Colonel Craig's exposition would the reviewer take issue—the question of the carrier and the alleged symptoms of the carrier state. In table II on page 45 is set forth the incidence of positive results of examinations of the stools as made by various workers in different parts of the country. The figure varies from 0.2 per cent in the series of Andrews and Paulson in Baltimore to 53 per cent among the students of the University of California as reported by Kofoid. Among a total of 49,336 persons studied in various surveys, 11.6 per cent harbored *Amoeba histolytica*, and this Craig believes to be a fair average figure. When one turns, however, to the symptoms which are said to result from the carrier state the situation is much less convincing. Indeed, the reviewer fears that Craig, firm in his belief, fails to see the weakness of his case when he states that carriers of amebas suffer from gas, constipation or diarrhea, disturbances of appetite, loss of weight, headache, sleepiness and disturbed slumber, poor memory, nervous instability, slight elevations of temperature or subnormal temperature, poor circulation (whatever that may mean), sallow skin and tenderness over the abdomen. Obviously this catalog would fit equally well a dozen other disorders, even such entirely unrelated ones as hypertension or chronic brucellosis. As the significance of the carrier of *Ameba histolytica* is the most important part of the whole problem of amebiasis from the standpoint of both individual and public health, one regrets that this subject has been dealt with somewhat from the standpoint of the special pleader.

**Studies on Blood Sugar and Glycosuria in Exophthalmic Goitre** By  
William Thune Andersen Pp 206, with 16 illustrations Copenhagen  
Levin & Munksgaard, 1933

This book contains the author's thesis for the doctorate of medicine at the University of Copenhagen. The material comprised thirty-one patients with exophthalmic goiter and two with diabetes mellitus. In one case of diabetes, exophthalmic goiter was associated, in the other, myxedema. The patients with exophthalmic goiter were examined systematically for spontaneous glycosuria and for the response of the blood sugar to injections of dextrose. By these means some abnormality was demonstrated in nearly all. Andersen concludes that in uncomplicated exophthalmic goiter the blood sugar during fasting is normal in most instances most of the time, but that an occasional higher than normal value during fasting is found in more than one half of the cases, and that the alimentary

blood sugar curve is increased in height and duration in most cases. Thyroidectomy is followed by a diminution in the abnormality of the alimentary blood sugar curve.

The renal threshold for dextrose in the patients with exophthalmic goiter may be slightly lower than normal, but typical renal glycosuria was not found in the patients studied. The threshold tended to rise after thyroidectomy. The patient with diabetes showed marked improvement in the diabetes following thyroidectomy, as has been repeatedly observed by other investigators in other patients.

Andersen inclines to the theory of Eppinger, Rudinger and Falta which was later abandoned by Falta that the thyroid directly inhibits the island mechanism of the pancreas and suggests that the thyroid product has a destructive effect on the island cells. An alternate theory that was presented at various times by Allen Fitz and Wilder, namely that carbohydrate tolerance is depressed by elevation of the rate of metabolism in diabetic patients with hyperthyroidism he rejects on the ground of old experiments of Freund and Marchand. These investigators in 1913 reported that when the cervical medulla was severed in animals so that regulation of heat was obviated and the metabolism was increased up to 100 per cent there was no demonstrable tendency to hyperglycemia, but it is scarcely necessary to point out that these experiments were not performed on diabetic animals that the accuracy of determinations of basal metabolic rates made in 1913 may well be questioned and that fever and increased rates of chemical exchanges are by no means synonymous. It is not to be presumed supposedly, that a dose of thyroid only large enough to bring the basal metabolic rate of a patient with myxedema up to normal would injure pancreatic cells. Yet in Andersen's patient with diabetes associated with myxedema the tolerance for carbohydrate was definitely depressed and the requirement of insulin correspondingly increased by doses of thyroid only large enough to raise the basal metabolic rate to normal.

**The Compleat Pediatrician** By Wilburt C. Davison M.A. D.Sc. M.D.  
Professor of Pediatrics, Duke University School of Medicine and Pediatrician, Duke Hospital, formerly Acting Head of Department of Pediatrics, the Johns Hopkins University School of Medicine, and Acting Pediatrician in Charge, the Johns Hopkins Hospital, Fellow, American Academy of Pediatrics and American College of Physicians, member, White House Conference American Pediatric Society and American Board of Pediatrics. Cloth Price, \$3.75  
Pp 262. Durham, N. C. Duke University Press 1934.

This unique work is an index to the practice of pediatrics. The author has wisely and perhaps necessarily included in the book a list of instructions for its use. When one opens the book haphazardly one is confronted by a mass of apparently unrelated words and symbols that become clear only after a perusal of these instructions.

Symptoms are set down, and each symptom is followed by a list of the diseases which may provoke it. The probable diseases are classified as very rare, rare, common and very common and one is referred by a symbol to the portion of the book in which the disease itself is discussed.

The consideration of the diseases is confined to an outline of diagnosis and treatment.

There is a further section on preventive measures and one on infant feeding. A chapter is devoted to laboratory methods.

The book represents a tremendous amount of work and should be of definite value to the student and the general practitioner. Davison naively states that a large number of patients either recover or succumb regardless of therapy and his objective is to encourage the recognition of those conditions in which therapy is of value. He has succeeded in putting a tremendous amount of information into a small space. He is known to be an excellent pediatrician and the title of his work would mark him as a fisherman even if he had not included as his title an adaptation of Izaak Walton's 'The Compleat Angler'.



**Das Beriberi Herz** By Prof K F Wenckebach Price, 12 marks Pp 106,  
with 38 illustrations Berlin Julius Springer, 1934

This little monograph is the result of observations by Professor Wenckebach made in the Netherland Indies, and such a study of a controversial subject by an expert cardiologist seems to the reviewer of great value. Actual myocardial lesions are described, and an interesting tendency to "right-sided failure" is emphasized. The pathologic and clinical features are discussed in detail, and the text is richly illustrated with photographs of specimens, roentgenograms and electrocardiograms. There is a full bibliography.

## CARDIAC OUTPUT AND RELATED FUNCTIONS UNDER BASAL AND POSTPRANDIAL CONDITIONS

A CLINICAL STUDY

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NEW YORK

Since the function of the heart is to pump into the arteries the blood received from the veins, there is perhaps no more pertinent question regarding cardiac action than the amount of blood which the heart pumps during a given time. That amount is usually designated as the minute volume or cardiac output and is conveniently expressed in liters per minute. In the normal adult of average size under basal conditions the cardiac output is about 4 liters per minute. This applies to either ventricle, since the output is the same for both sides. With a pulse rate of 70 per minute, the systolic output averages 60 cc., or about 2 ounces.

The intimate relation of the digestive and circulatory systems is indicated by the influence of digestion on the pulse rate, blood pressure, circulation time and cardiac output. The pulse rate<sup>1</sup> and the systolic blood pressure are found to increase after eating, while the diastolic pressure may show a slight decrease<sup>2</sup>. The circulation time of the blood in dogs was studied by Sheard, McCracken and Essex<sup>3</sup> by injecting radium C into the jugular vein and measuring the time which elapsed before its arrival in the femoral artery, as detected by a radio-sensitive electroscope. "The results of the investigation show that the circulation time of the blood in dogs previously fasted is reduced 20 to 35 per cent during the digestion of a mixed meal." It should be noted that a determination of the circulation time gives the time consumed by the fastest moving particles in the blood stream while traveling from one arbitrarily chosen point to another. This may or may not be a

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1 Rihl, J. Die Frequenz des Herzschlages, in Bethe, A., von Bergmann, G., Emden, G., and Ellinger, A. Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol 7, p 449

2 Janeway, T. C. The Clinical Study of Blood Pressure, New York, D Appleton and Company, 1904

3 Sheard, C., McCracken, E. C., and Essex, H. E. The Circulation Time of the Blood in Dogs Before and During the Digestion of Food, Am J Physiol 109 96, 1934

linear function of the average rate of flow. Although it gives no quantitative idea of the amount of blood circulating through the vessels or even of the average rate of flow (since the velocity in the center of the stream is greater than that at the periphery), it is useful in detecting relative changes.

Herrick and her associates<sup>4</sup> applied the thermostromuhr method of Rein to study the effect of digestion on the rate of flow in the femoral, carotid and mesenteric arteries and the external jugular vein. These authors stated

contrary to current belief we have found that blood is not diverted from the somatic tissue to the visceral organs during the digestion of food. Instead of a decrease in blood flow in the femoral and carotid arteries and jugular vein, there is a marked prolonged increase during the digestive cycle. This is likewise true in the mesenteric artery.

They found that during the third hour after digestion starts the blood flow in the femoral artery may be double the basal value. This doubling of the blood flow seems inordinately large as compared with the results of other workers as well as with the subsequent findings of Herrick and her collaborators,<sup>5</sup> who studied the effect of digestion of food on the liver of the dog and reported an average increase in the blood flow of about 54 per cent.

#### DIGESTION AND CARDIAC OUTPUT

In man, the effect of digestion on the cardiac output was studied in one subject by Jarisch and Liljestrand,<sup>6</sup> in six by Kisch and Schwarz<sup>7</sup> and in six by Grollman.<sup>8</sup> All these workers found an increase in the cardiac output. Grollman, who made the most extensive study, reported that "the cardiac output rises immediately after the ingestion of food, reached a maximum of 0.5 to 2.0 liters over the fasting level, and remains at this high and practically constant level for one to three hours."

These studies of the effect of digestion on the circulation in the dog and in normal man have been sufficiently illuminating to warrant

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4 Herrick, J. F., Essex, H. E., Mann, F. C., and Boldes, E. J. The Effect of Digestion on the Blood Flow in Certain Blood Vessels of the Dog, *Am J Physiol* **108** 621, 1934.

5 Herrick, J. F., Mann, F. C., Essex, H. E., and Boldes, E. J. The Effect of the Digestion of Food on the Blood Flow from the Liver of the Dog, *Am J Physiol* **109** 52, 1934.

6 Jarisch, A., and Liljestrand, G. Ueber das Verhalten des Kreislaufes bei Muskelarbeit, nach dem Essen, und bei Flüssigkeitszufuhr, *Skandinav Arch f Physiol* **51** 235, 1927.

7 Kisch, B., and Schwarz, H. Das Herzschlagvolumen und die Methodik seiner Bestimmung, *Ergebn d inn Med u Kinderh* **27** 169, 1925.

8 Grollman, A. The Effect of the Ingestion of Food on the Cardiac Output, Pulse Rate, Blood Pressure, and Oxygen Consumption of Man, *Am J Physiol* **89** 366, 1929.

their extension to an investigation of patients having some circulatory abnormality. I report, therefore, the results of forty-four determinations of the cardiac output and related functions made under basal and postprandial conditions in twelve subjects, five of whom had normal cardiovascular systems while seven presented some structural or functional abnormality. In determining the cardiac output I used the acetylene method as described by Grollman.<sup>9</sup>

The question of the technic of the clinical determination of the cardiac output has stimulated a tremendous amount of effort, which is doubtless justified by its importance and is described in a voluminous literature. A short historical statement is offered to assist in the comprehension and critical evaluation of the method used in this study. During the past sixty years the problem of determining the cardiac output in man has been attacked in several ways. The first method was the attempt to estimate the cardiac output in man by making direct measurements on experimental animals and assuming the existence of some ratio based on the size of the heart and ventricles in man as compared with those of the animals studied.<sup>10</sup> These methods have no special clinical interest, but one is surprised to learn how well these indirect results compare with the later findings.

The second method is based on the important fact pointed out by Fick,<sup>11</sup> in 1870, and often called the Fick principle. If one measures the concentration of carbon dioxide or oxygen in the venous and arterial blood, one can determine the volume of oxygen taken up by each liter of blood as it passes through the lungs, as well as the volume of carbon dioxide given off. One can then, by means of a spirometer, determine the total volume of carbon dioxide given off or the total volume of oxygen consumed during one minute and can calculate the number of liters of blood that must have passed through the lungs to account for the liberation of the observed amount of carbon dioxide or the consumption of the observed amount of oxygen. In making this determination the arterial blood may be obtained from one of the peripheral arteries such as the brachial, while the venous blood must be obtained from the right side of the heart, because only here does one obtain an aliquot sample of mixed venous blood. The gaseous content of specimens of venous blood obtained from peripheral veins varies with the metabolic activity of the local area drained. This method of determining the cardiac output is so direct and so reliable that it has

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9 Grollman, A. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas Publisher, 1932.

10 Tigerstedt, R. *Die Geschwindigkeit des Blutes in den Arterien*, *Ergebn d. Physiol.* 4: 481, 1905.

11 Fick, A. *Ueber die Messung des Blutquantums in den Herzventrikeln*, *Sitzungsb. d. phys.-med. Gesellsch. zu Würzburg*, 1870, p. 16.

been used as a basis of comparison for testing the validity of other, less direct, methods. The objection to cardiac puncture has restricted the use of the method to experiments on animals. Recently, however, Baumann<sup>12</sup> and his co-workers applied the method to man and provided the means of testing the many indirect methods that have been used in determining the cardiac output in man. In order to avoid the necessity of arterial and cardiac punctures, many indirect breathing methods for obtaining the carbon dioxide concentration in arterial and venous blood have been suggested, but these methods have usually yielded inconsistent results and have proved inferior to the use of the foreign gas method, which is the third method that I shall consider.<sup>a</sup>

The foreign gas method was first attempted by Bornstein,<sup>13</sup> in 1910, when nitrogen was used without much success. The use of nitrogen monoxide was suggested the following year by Markoff, Muller and Zuntz.<sup>14</sup> This gas was then used by Krogh and Lindhard,<sup>15</sup> their method was modified by Marshall and Grollman,<sup>16</sup> who used ethylene as the foreign gas, until after further studies Grollman<sup>17</sup> found acetylene to be superior. A description of this method will suffice to illustrate the principles on which most of the foreign gas methods are founded.

The patient whose cardiac output is to be determined is permitted to breathe into and out of a 3 liter rubber breathing-bag containing a mixture of air and acetylene. The nose is compressed with a clip so that the lungs and bag form a closed system. After fifteen seconds of rebreathing to insure complete mixture, a sample of gas is admitted to an evacuated sampling tube. The patient continues to breathe into and out of the bag, and after from six to eight seconds another sample of gas is taken. During the few seconds which elapse between the drawing of the samples the composition of the mixture of gases has changed. Oxygen and acetylene have been in part absorbed by the blood passing through the lungs, and carbon dioxide has been given off. The two samples of gas are then analyzed to determine the extent to which the various gases have changed in concentration.

The purpose of this rebreathing procedure is to determine the arteriovenous difference for oxygen. For example, if one finds that 1 liter of arterial blood contains 60 cc more oxygen than 1 liter of venous blood, a liter of blood must

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12 Baumann, H. Ueber die wahre Grosse des Minutenvolumens, *Verhandl d deutsch Gesellsch f inn Med* **42** 247, 1930.

13 Bornstein, A. Eine Methode zur vergleichenden Messung des Herzschlagvolumens beim Menschen, *Arch f d ges Physiol* **132** 307, 1910.

14 Markoff, I., Muller, F., and Zuntz, N. Neue Methode zur Bestimmung der im menschlichen Korper umlaufenden Blutmenge, *Ztschr f Balneol* **4** 373, 409 and 441, 1911.

15 Krogh, A., and Lindhard, J. Measurements of the Blood Flow Through the Lungs of Man, *Skandinav Arch f Physiol* **27** 100, 1912.

16 Marshall, E. K., and Grollman, A. A Method for the Determination of the Circulatory Minute Volume in Man, *Am J Physiol* **86** 117, 1928.

17 Grollman, A. The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am J Physiol* **88** 432, 1929.

take up 60 cc of oxygen while it passes through the lungs. One then measures the oxygen consumption, and if it proves to be 240 cc of oxygen per minute it is apparent that  $\frac{240}{60}$ , or 4 liters, of blood is passing through the lungs in one minute. The cardiac output, therefore, is calculated from the oxygen consumption and the arteriovenous oxygen difference. The oxygen consumption may be measured by means of the spirometer used for the determination of the basal metabolism. The arteriovenous difference is calculated from the change in concentration of the gases found in the two samples. Why is a foreign gas, such as acetylene, used in determining the arteriovenous difference for oxygen? The arteriovenous difference is simply another expression for the amount of gas which a liter of blood takes up or gives off while passing through the lungs. A foreign gas like acetylene is used because venous blood coming to the lungs contains none of this gas, and the amount taken away depends merely on the solubility of that gas in the blood. The amount of gas taken up indicates the arteriovenous difference for acetylene. While the blood passing through the lungs is taking up acetylene, it is also taking up oxygen. If it takes up the same amount of oxygen as acetylene, the arteriovenous difference is the same for both. Usually the amounts of the two gases are different but the arteriovenous oxygen difference can be calculated from the ratio of the amounts of the two gases absorbed. The determination must be finished within twenty-three seconds, otherwise, the blood laden with acetylene will make a complete circuit of the body and come back to the lungs. Such blood, containing acetylene, will not be able to absorb the requisite amount of gas from the alveolar spaces. It is apparent that the entire calculation is based on the change in concentration of the gases during the few seconds which elapse between the drawings of the samples. Since the change in concentration is small, any errors in the analysis of the gases will be proportionately large. An error of 0.03 per cent in this analysis may produce a 3 per cent error in the arteriovenous difference and the cardiac output.

In making my determinations I followed the technic as described by Grollman<sup>9</sup> but made a change in the method of analysis of the gases which lowers the arteriovenous difference and increases the result for the cardiac output approximately 3 per cent. The equation for the arteriovenous oxygen difference is as follows:

$$\text{Arteriovenous difference} = \frac{(\text{difference for oxygen}) (\text{average for acetylene}) (B-48.1) (0.00974)}{\text{difference for acetylene}}$$

The arteriovenous oxygen difference is finally given in cubic centimeters of oxygen per liter of blood. In the numerator the oxygen difference represents the difference in concentration of the oxygen in the two samples; the average for acetylene is the average concentration of acetylene in the two samples, and B is the barometric pressure. In the denominator, the acetylene difference is the difference in the concentration of the acetylene in the two samples. During the interval between the drawing of the samples the volume of oxygen plus the amount of acetylene absorbed exceeds the volume of carbon dioxide excreted by the blood, resulting in a net decrease in the volume of the lung-bag system. This tends to make the percentages of the gases in the second sample too high or those in the first sample too low for comparison. The necessary correction is made by increasing the values found in the first sample proportionately to the increase found in the percentage of nitrogen which presumably takes no part in the transepithelial gaseous interchange. For the derivation of the equation just given as well as of the principles and assumptions on which it is based, the reader is referred to Grollman's excellent monograph.<sup>9</sup>

The results of an analysis of a pair of samples is given, and the calculation for the arteriovenous difference is indicated

	Sample 1	Sample 1 (Corrected)	Sample 2	Difference (Percentage)
Carbon dioxide	5 37		5 98	
Acetylene	10 71	11 06	9 16	1 90
Oxygen	15 30	15 79	14 03	1 76
Nitrogen	68 62		70 83	

$$\text{Arteriovenous difference} = \frac{(1.76) (9.94) (760.481) (0.00974)}{1.90} = 63.8$$

The percentage composition of the mixtures of gases is found by introducing a known amount of gas into the buret of a modified Haldane apparatus and measuring the volume of the gas which remains after the successive removal of carbon dioxide, acetylene and oxygen, in the order named. The final volume of gas consists of nitrogen. For removing carbon dioxide a 10 per cent solution of potassium hydroxide saturated with sodium chloride is used, for acetylene a solution of an alkaline cyanide, and for oxygen an alkaline solution of pyrogallol. Grollman stated that acetylene is slightly soluble in the solution of potassium hydroxide, which results in a slight absorption of acetylene during the removal of carbon dioxide. Since the difference for acetylene would not be effected if the small error were equal in both analyses, Grollman recommended that during the analysis of each sample the gas be forced into the carbon dioxide absorber an equal number of ("eight or more") times. "One thus avoids the solution of an unknown and different amount of acetylene in successive samples."<sup>9</sup>

Although during the removal of carbon dioxide there is not sufficient time for the establishment of acetylene equilibrium as between the solution of potassium hydroxide and the overlying mixture of gases, nevertheless the amount of acetylene dissolved depends on the time of exposure, the pressure within the absorbing chamber, the temperature of the environment and other factors. Even though all the other factors are kept constant, the two samples differ in their concentration of acetylene, with a resulting increase in the partial pressure of the acetylene of the first sample as compared with that of the second. This would lead to a greater solution of acetylene during the absorption of carbon dioxide in the first, as compared with the second, analysis. This can be demonstrated by repeating the absorption in the potassium hydroxide after the carbon dioxide is removed. A small amount of acetylene will be dissolved. This is the equivalent of making a blank determination to see how much acetylene is absorbed under the physical conditions of the analysis. I found that the amount of acetylene absorbed during ten exposures in potassium hydroxide is less during the second than during the first exposure and less during the third than the second, etc. It is safe to assume that the amount of acetylene absorbed during ten exposures in potassium hydroxide at most equals but does not exceed the amount absorbed in the previous exposure. In analyzing my samples, therefore, I forced the mixture of gases into potassium hydroxide ten times. This is sure to absorb all the carbon dioxide and a small amount of acetylene. After the reading is taken the remaining mixture of gases is again forced into potassium hydroxide ten times in the same way. In this procedure a small amount of acetylene is absorbed. The second absorption of acetylene is always greater in the first sample than in the second, because the partial pressure of acetylene is higher in the first. This disparity confirms the theoretical conclusion already expressed that the small amount of acetylene absorbed in the samples during the removal of carbon dioxide is different because of the different partial pressure of the gas. The error involved can be partly corrected by subtracting the volume of acetylene absorbed during the second ten exposures

from the volume of carbon dioxide plus acetylene absorbed during the first ten exposures. When this is done, the determination already described would yield the following results:

	Sample 1	Sample 1 (Corrected)	Sample 2	Difference (Percentage)
Carbon dioxide	5.16		5.86	
Acetylene	10.92	11.27	9.28	1.99
Oxygen	15.30	15.79	14.03	1.76
Nitrogen	68.62		70.83	

$$\text{Arteriovenous difference} = \frac{(1.76)(10.10)(760.481)(0.00974)}{1.99} = 61.9$$

The correction indicates that the average for acetylene should be 10.10 instead of 9.94 and the difference for acetylene should be 1.99 instead of 1.90 per cent. Since one factor is in the numerator and the other is in the denominator, the two errors offset each other partly but not entirely, as is seen in the final result.

It is interesting to note that in the nine cases reported by Baumann and Grollman,<sup>18</sup> who compared the results of the acetylene method with those of the Fick principle, using the direct puncture of the right ventricle, the results in five instances agree within 2 to 3 per cent, and that in four of these five cases there was the slightly lower cardiac output which the principles just stated would lead one to expect from the method of analysis originally described.

In a personal communication to me regarding the findings just described, Dr. Grollman stated that the error discussed is theoretically possible but in his studies did not exceed 1 per cent. I found that the acetylene is more soluble in 10 per cent potassium hydroxide (saturated with sodium chloride) than in a saturated solution of potassium hydroxide but that the high viscosity of the latter renders it less sensitive to slight changes in pressure and less suitable for measuring changes in volume. The amount of acetylene absorbed varies with the number of times the mixture of gases is forced into potassium hydroxide. The amount of acetylene absorbed by potassium hydroxide is also somewhat greater when the solutions are cold than when they are warm. Because of these variable factors which influence the size of the analytic error, I believe that in performing these analyses it is important, first, to realize that an error is possible and, second, to determine its size and correct it. The size of the error is indicated in any individual analysis by the simple corrective procedure here described.

In studying the effect of digestion on the cardiac output, in most cases, I acquainted the subject with the complete procedure by making a test on the day before the experiment in order that the rebreathing be properly performed and the peculiar taste as well as the innocuousness of the acetylene become familiar. On the following morning the cardiac

<sup>18</sup> Baumann, H., and Grollman, A. Ueber die theoretischen und praktischen Grundlagen und die klinische Zuverlässigkeit der Acetylen Methode zur Bestimmung des Minutenvolumens, *Ztschr. f. klin. Med.* **115** 41, 1930.



Data on Effect of Digestion on the Cardiac Output Under Basal and Postprandial Conditions

Determination	Date, 1934	Subject	Diagnosis	Age, Years	Sex	Height, Inches	Weight, Pounds	Condition During Test	Pulse Rate		Blood Pressure		Oxygen Consumption, Cc per Minute	Relative Value of Oxygen Consumption	Arteriovenous Oxygen Difference, Cc per Liter of Blood	Cardiac Output, Liters per Minute	Cardiac Index	Relative Value of Cardiac Output	Systolic Output, Cc	$\frac{S-D}{\frac{1}{2}(S+D)}$	Ratio of Systolic Output $R \times \frac{S-D}{\frac{1}{2}(S+D)}$
									Systolic	Diastolic	Systolic	Diastolic									
1	4/18	I L	Normal	22	M	69	149½	Basal	54	112	72	230	100	61.3	3.57	1.97	100	99	435	659	235
2	4/19							2 hr post prandial	60	130	60	291	127	65.6	4.43		124	71	736	995	442
3								3 hr post prandial	60	128	65	276	120	67.1	4.11		115	69	653	916	302
4	5/24	L T	Normal	25	M	71	165	Basal	58	105	70	213	100	53.7	3.97	2.02	100	69	400	580	232
5								Basal	52	100	70	220	103	50.1	4.39		127	81	353	426	181
6	5/23							2 hr post prandial	60	110	65	270	127	53.6	5.04		127	81	514	612	408
7								4 hr post prandial	55	105	75	248	117	50.1	4.96		125	90	333	370	181
8	4/20	W S	Normal	17	M	67	142	Basal	56	112	58	222	100	61.3	3.62	2.09	100	65	636	979	376
9	4/21							2 hr post prandial	63	115	58	270	122	62.8	4.29		119	68	677	967	414
10								3 hr post prandial	63	115	62	272	123	57.4	4.73		131	75	598	798	377
11	4/13	A F	Colitis	13	M	64	101	Basal	86	105	55	175	100	49.0	3.57	2.46	100	42	625	149	537
12	12/5/7							2 hr post prandial	80	95	50	206	118	52.1	3.95		111	40	620	127	512
13								3 hr post prandial	84	96	50	[206]	115	46.1	4.61		129	55	630	115	529
14	4/30	M B	Duodenal ulcer	34	M	68	132	Basal	72	108	70	208	101	59.7	3.49	2.05	100	48	427	889	307
15								Basal	72	110	68	205	100	52.1	3.94		147	55	472	858	340
16	5/1							2 hr post prandial	80	110	60	280	135	54.7	5.12		147	64	588	920	470
17								3 hr post prandial	72	110	62	221	108	51.0	4.33		124	60	559	932	403
18	6/1	A N	Exophthalmic goiter	43	M	69	131	Basal	82	125	60	307	100	52.0	5.92		100	72	702	976	576
19								1½ hr post prandial	90	132	55	324	106	54.0	6.01		102	67	824	1,230	742
20	6/2							Basal	80	120	60	289	100	55.7	5.19	3.04	100	65	667	1,025	531
21								1 hr post prandial	82	130	50	300	104	54.1	5.51		107	68	889	1,307	729
22	6/9	D L	Exophthalmic goiter	37	M	65	119	Basal	92	130	60	283	100	56.3	5.93	2.20	100	55	737	1,340	677
23								1 hr post prandial	96	140	40	302	107	57.9	5.22		104	54	1,111	2,042	1,066
24	6/8							1½ hr post prandial	96	135	30	312	110	55.1	5.66		112	59	1,230	2,183	1,388
25								5½ hr post prandial	96	135	55	298	105	57.0	5.23		104	55	812	1,532	808
26	5/18	H C	Hypertension, angina pectoris, thyrotoxicosis, hypothyroidism	38	M	69	142	Basal	50	130	90	164	100	65.9	2.49	1.11	100	50	364	728	182
27								Basal	52	135	95	181	110	72.8	2.49		137	48	318	725	181
28	5/17							1½ hr post prandial	55	150	90	195	119	67.1	3.42		137	62	500	806	275
29								2 hr post prandial	75	228	138	289	117	62.5	3.66		123				
30	5/22	A H	Essential hypertension	51	M	66½	142	6 hr post prandial	75	228	138	289	117	62.5	3.66		123	71	492	667	768
31								3 hr post prandial	76	230	130	320	124	63.1	5.53		75	75	536	741	423
32	5/21							1 hr post prandial	80	230	130	337	124	63.1	6.35		79	576	704	449	
33	6/5	L F	Hypertension, coronary sclerosis	45	M	69	135	Basal	72	185	120	230	100	59.1	3.89	2.25	100	54	426	789	306
34								1 hr post prandial	75	145	80	279	121	49.0	5.70		147	76	578	761	433
35	6/6							Basal	72	190	120	210	100	60.9	3.45		100	48	452	940	325
36								1 hr post prandial	75	150	85	222	106	52.3	4.25		123	57	553	970	418
37	5/31	H C	Arteriosclerotic heart disease	62	M	69	140	Basal	62	90	60	197	100	55.1	3.39	1.94	100	53	400	728	248
38								6 hr post prandial	66	100	68	202	102	64.1	3.15		100	48	381	793	251
39	5/29							1½ hr post prandial	66	95	55	215	124	62.9	3.80		115	59	534	905	352
40	5/11	G S	Syphilitic aortitis, aortic insufficiency, rheumatic (?) mitral disease	34	M	65	124	Basal	58	100	40	191	100	60.8	3.14	1.96	100	54	837	1,588	497
41	5/14							Basal	58	100	45	191	100	59.3	3.22		55	759	1,380	440	
42	42							Basal	59	110	45	205	107	65.4	3.14		63	839	1,583	495	
43	5/15							2 hr post prandial	60	110	40	226	118	64.2	3.52		112	59	833	1,650	560
44								3 hr post prandial	60	118	35	223	117	65.0	3.43		109	57	806	1,572	578

output was determined under basal conditions. A rather full breakfast, consisting in most instances of fruit, cereal, two eggs, toast and coffee, was given. The test was then repeated from one to three hours after the meal. In some cases, as is indicated by the dates in the table, the tests carried out under basal conditions and those carried out under postprandial conditions were performed on successive or different days. All the patients studied were lying comfortably in bed. With only one or two exceptions, the subject was permitted to lie quietly in bed for a full hour or more before a test was performed, in order to insure complete physical rest. The blood pressure was determined by the auscultatory method<sup>19</sup> with the aid of a mercury manometer. If good checks were not obtained on successive readings, the determination was repeated.

The results are shown in the table. In summarizing these findings I shall mention the general results common to all or most of the subjects and then consider the peculiar individual variations or points of interest noted. During digestion, as compared with the fasting condition with the patient at rest, there is a slight increase in the pulse rate together with an increase in the systolic pressure and usually a less marked fall in the diastolic pressure, resulting in an increase in the pulse pressure. The oxygen consumption, as is well known, increases during digestion. The individual increments, as observed from one to three hours after eating, vary in the normal subject from 18 to 35 per cent and average 25 per cent above the values during fasting. In the abnormal subject the increments vary from 4 to 24 per cent, and the average increase is only 13 per cent. From one to three hours after eating the cardiac output in the normal subject increases by from 11 to 47 per cent above the value during fasting, with an average of 25 per cent. In the abnormal subject the increments vary by from 2 to 47 per cent, the average increase being 17 per cent. Five or six hours after eating the cardiac output approximates the value during fasting. The cardiac index designates the basal cardiac output per square meter of body surface and in normal persons equals  $2.2 \pm 0.3$ <sup>9</sup>. The systolic output, which is found by dividing the cardiac output by the pulse rate, increases during digestion because the cardiac output shows a greater relative increase than the pulse rate.

The extra demands made on the heart during digestion, especially after a large meal, give some clue to an understanding of the well established clinical observations that overeating by patients with cardiac disease often leads to discomfort and exacerbation of symptoms and

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<sup>19</sup> Gladstone, S. A. Concerning the Mechanism of Production of the Korotkoff Sounds and Their Significance in Blood Pressure Determinations, *Bull Johns Hopkins Hosp* **44** 122, 1929.

occasionally to death. The last is sometimes erroneously ascribed to "acute indigestion." The physiologic basis for decreasing the size of the feeding in the treatment of heart failure, as exemplified by the usual cardiac low caloric diet, is also evident.

The low pulse rate (54, 58, 52 or 56 per minute) observed in normal young adults in the fasting condition and completely at rest is worthy of note. The pulse rate usually observed during routine examination is almost invariably considerably higher and indicates to what extent the subject's condition diverges from complete mental relaxation and physical rest.

In striking contrast to the general trend of changes in the blood pressure during digestion are those observed in patient E. F. (experiments 33 to 36). A marked fall is observed in both the systolic and the diastolic pressure during digestion. The extent of the change is practically the same, as observed on two successive days. Further studies will be necessary to determine the significance of these findings. The high cardiac index in patients with exophthalmic goiter<sup>9</sup> indicates the high cardiac output in that condition. Contrariwise, the cardiac index is very low in subject H. C. (experiments 26 to 29), whose hypothyroidism resulted from thyroidectomy for angina pectoris as recommended by Blumgart and his co-workers<sup>20</sup>. It may be noted in the case of the abnormal subject that while the average increase of oxygen consumption produced by digestion was 13 per cent, in the four observations on patients with exophthalmic goiter the average was only 7 per cent. A similar difference is noted in the results of the determinations of the cardiac output. This can be explained partly on the basis of the high initial figures during fasting, to which the increments are compared, but a better understanding of this difference will have to await a more extensive and detailed study.

#### CARDIAC OUTPUT AND BLOOD PRESSURE

Numerous investigators have studied the correlation of the cardiac or systolic output with measurable physical changes which occur during the heart's contraction in an attempt to use these changes as an index of the amount of blood discharged by the heart. The systolic output has been studied in relation to plethysmographic changes or changes in volume of the arm,<sup>10</sup> roentgen changes in the size of the heart,<sup>21</sup>

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20 Friedman, H. F., and Blumgart, H. L. Treatment of Chronic Heart Disease by Lowering Metabolic Rate, Necessity for Total Ablation of Thyroid, *J. A. M. A.* **102** 17 (Jan 6) 1934.

21 Eyster, J. A. E., and Meek, W. J. Instantaneous Radiographs of the Human Heart at Determined Points in the Cardiac Cycle, *Am. J. Roentgenol.* **7** 471, 1920.

changes in the blood pressure<sup>22</sup> and other changes. Of particular clinical interest are the studies correlating the systolic output with changes in the blood pressure, because of the ease and frequency with which the blood pressure is clinically determined. In 1904, Erlanger<sup>23</sup> found that the average of a large number of determinations of the volume of the arm and hand indicated that the pulse pressure and the changes in volume produced by the beat of the heart vary directly, "Exceptions, probably the result of local vaso-motor changes, are occasionally seen." Four years later, Dawson and Gorham<sup>24</sup> reported the results of simultaneous cardioplethysmographic measurements of the systolic output and manometric records of changes in the arterial blood pressure in anesthetized dogs before and during various procedures to alter the systolic output (stimulation of the central and peripheral branches of the vagus, stimulation of peripheral nerves, infusion of saline solution, bleeding, asphyxia and other methods). These authors concluded that "the pulse pressure is a reliable index of the systolic output." Regarding these two factors, first, it is apparent from a study of the graphs and tables presented by these workers that a change in one of these factors is usually attended by a change in the other in the same direction, i. e., an increase or a decrease. Secondly, it is equally apparent that the extent of the change in one factor is not equal or proportional to the extent of the change in the other, i. e., there is no simple linear relation between the two. Such relationship as may exist must be influenced by other factors, such as the variable elasticity of the aorta in different persons and also, in the same subject, the progressively decreasing distensibility of the aorta as it is stretched by a force which is serially increased by equal increments. In short, the more the aorta is stretched the harder it is to stretch it further. Furst and Soetbeer<sup>25</sup> studied the relation between volumetric filling of the aorta and the pressure produced at various stages of distention. This was done by filling the aorta with fluid, after tying off all the branch vessels, and measuring the increase in pressure produced by forcing additional measured amounts of fluid into the aorta. These authors

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22 Liljestrand, G., and Zander, E. Vergleichende Bestimmungen des Minutenvolumens des Herzens beim Menschen mittels der Stickoxydulmethode, und durch Blutdruckmessung, *Ztschr f d ges exper Med* **59** 105, 1928.

23 Erlanger, J., and Hooker, D. R. An Experimental Study of Blood Pressure and Pulse Pressure in Man, *Johns Hopkins Hosp Rep* **12** 145, 1904.

24 Dawson, P. M., and Gorham, L. W. The Pulse Pressure as an Index of the Systolic Output, *J Exper Med* **10** 484, 1908.

25 Furst, T. and Soetbeer, F. Experimentelle Untersuchungen über die Beziehungen zwischen Füllung und Druck in der Aorta, *Deutsches Arch f klin Med* **90** 190, 1907.

offered the following formulas, which were empirically derived, as expressing the relationship of the various factors

$$(1) V = \frac{P}{D + \frac{P}{3}}$$

$$(2) V = \frac{P}{D + \frac{P}{2}}$$

V, is the increase in volume (systolic output), P, the increase in pressure (pulse pressure), and D, the initial or minimal pressure (diastolic pressure) Although the original authors considered the second formula less satisfactory, Liljestrand and Zander,<sup>22</sup> in 1928, studied its variations as well as the changes in the cardiac and systolic output in four persons at rest, after eating, after the injection of epinephrine hydrochloride and during exercise They found a satisfactory correlation between the systolic output as calculated from the second equation and the output as determined by the nitrogen monoxide method In 1931, Schoenewald<sup>26</sup> studied the cardiac output and the changes in blood pressure during and following exercise in ten normal subjects and seventeen subjects with pathologic conditions and found that there was no constant relationship between the cardiac output as determined by the acetylene method and the output as calculated by the blood pressure formula, Bornstein, Budelmann and Ronnell<sup>27</sup> studied the changes produced by hot and cold baths on the cardiac output and blood pressure and observed that the "otherwise satisfactory" relationship between the pulse pressure and the stroke volume did not obtain They believed that the disagreement was due at least partly to the particular influence of the hydrostatic pressure in baths

Since I made several determinations of the blood pressure and cardiac output in the same patient, I can examine my data to determine whether in any given person the systolic output as found by the foreign gas method is proportional to the systolic output as calculated from the blood pressure In order to compare my results with those of Liljestrand and Zander, I tabulated the numerical value for the systolic output as obtained from the formula  $\frac{S-D}{\frac{1}{2}(S+D)}$ , in which S is the systolic pressure in millimeters of mercury and D the diastolic pressure This value, multiplied by the pulse rate— $PR \times \frac{S-D}{\frac{1}{2}(S+D)}$ —is a similar numerical measure of the cardiac output, as shown in the table If a proportionality exists, the figures for the ratio, as shown in the table, should be con-

26 Schoenewald, G Ueber Beziehungen des Blutdrucks, besonders des Amplitudenfrequenzprodukts, zum Minutenvolumen des Herzens beim Menschen, Ztschr f d ges exper Med **79** 413, 1932

27 Bornstein, A, Budelmann, G, and Ronnell, S Minutenvolumen des Herzens in Baden, Ztschr f klin Med **118** 596, 1931

stant or approximately so in any given subject. It is apparent that strict proportionality is not observed. Since the probable error in the determination of the cardiac output may be 10 per cent and the error in the measurement of the pulse rate and blood pressure somewhat less, real relationships may be obscured as a result of cumulative errors, especially since the changes of the phenomena measured as expressed in percentages are not great. As compared with the changes produced by exercise or recovery from exercise, the changes caused by digestion are less suitable because they are proportionately smaller, but are more suitable in that they change slowly and give the examiner time to perform the various maneuvers necessary to obtain the desired data or even to repeat the determinations under approximately the same conditions. I believe that the inadequacy of the formula is due in part, at least, to the variations in the ejection time of the heart, variations in local vasomotor responses, variations in the amount of blood escaping from the arterial tree peripherally during systole and other factors. One would scarcely hope to describe accurately the physical changes in a *variable* hemodynamic system by means of a formula such as that of Furst and Soetbeer, which is empirically derived from data obtained in a more or less *constant* hydrostatic set-up. Nevertheless, other conditions remaining the same, an increased systolic output increases the pulse pressure. In a variable cardiovascular system, however, where local and general changes and readjustments are constantly taking place, these may be sufficient not only to alter the relationship between the pulse pressure and the systolic output but even to reverse it, as the findings made thus far strongly suggest.

Since the general effect of digestion is to increase the cardiac output, pulse rate and pulse pressure, it becomes evident that in these observations a pulse rate  $\times$  pulse pressure expression will increase with the cardiac output. Allowing for occasional experimental errors, this is seen to be true in practically all instances, i. e., the formula for the cardiac output indicates the direction of the change—an increase or decrease—as observed in the same person under approximately the same physical conditions, but the formula is not reliable as a quantitative measure of the change in the cardiac output and is even less reliable as a measure of the changes in the systolic output.

#### SUMMARY

The acetylene method was applied in a study of the effect of digestion on the cardiac output in forty-four determinations on twelve subjects, five of whom had normal cardiovascular systems while seven presented some structural or functional abnormality. A source of error in the method of analysis of gases as originally proposed is discussed, a cor-

rective procedure was applied, resulting in a tendency to increase the results for the cardiac output by approximately 3 per cent. As compared with the fasting condition, the effect of digestion on the circulatory system, as observed from one to three hours after taking a mixed meal of moderate size, consists in a slight increase in the systolic pressure and usually a less marked fall in the diastolic pressure, resulting in an increase in the pulse pressure. The cardiac output in the normal subject increased by from 11 to 47 per cent above the value during fasting, with an average increase of 25 per cent. In the abnormal subjects the increments varied by from 2 to 47 per cent, the average increase being 17 per cent. Several atypical responses in the subjects with pathologic conditions were noted.

The attempts to correlate changes in the blood pressure with changes in the systolic output are discussed, and the formula derived by Furst and Soetbeer and tested with varying results by several authors was found on application to our data to possess only limited usefulness.

Dr. B. S. Oppenheimer's helpful suggestions and stimulating interest made these studies possible.

# INCREASE IN CIRCULATION RATE PRODUCED BY EXOPHTHALMIC GOITER

COMPARED WITH THAT PRODUCED IN NORMAL SUBJECTS  
BY WORK

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In 1870, Frick pointed out that the output of the heart per minute could be determined from the difference in either the carbon dioxide or the oxygen tension of the blood before and after it passed through the lungs by direct determination of these gases in the arterial and venous blood. Subsequently, many attempts to adapt the Frick principle to the determination of the circulation rate in man were made by various investigators. The first of these attempts were based on equilibration of either the oxygen or the carbon dioxide in the lungs with the oxygen or the carbon dioxide in the blood, thus avoiding the dangers inherent in direct cardiac puncture as used originally. Bornstein, in 1910, suggested the use of high concentrations of nitrogen for equilibration, instead of carbon dioxide or oxygen, because it is an inert gas which does not enter into the various metabolic processes.

The next step was to use as the equilibrating medium not only an inert, but also a foreign, gas, nitrous oxide was suggested for this purpose by Markoff, Mueller and Zuntz, in 1911. The first successful method in which nitrous oxide was used was that developed by Krogh and Lindhard, which was reported in 1912. Krogh and Lindhard's method was first used in this country by Means and Newburgh<sup>1</sup> and by one of us (Boothby<sup>2</sup>), both investigations were reported in 1915. Means and Newburgh carried out studies on the effect of work on the circulation rate, and also made studies on patients with cardiac disease. Boothby limited his studies to the effect of work with himself as the subject and presented a chart illustrating the correlation

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1 Means, J H, and Newburgh, L H. Studies of the Blood Flow by the Method of Krogh and Lindhard, *Tr A Am Physicians* **30** 51, 1915

2 Boothby, W M. A Determination of the Circulation Rate in Man at Rest and at Work. *The Regulation of the Circulation*, *Am J Physiol* **37** 383 (May) 1915



of the circulation rate, pulse rate, respiration rate, ventilation rate and mixed venous carbon dioxide and oxygen tensions for increasing amounts of work as measured by oxygen consumption. Since then only four studies have been made which can be readily utilized for comparison.

In figure 1 are plotted the circulation rates of different normal subjects at varying degrees of muscular work, as well as the values for the same subjects at rest, taken from the studies by Bock, Vancaulaert, Dill, Folling and Hurxthal,<sup>3</sup> Boothby,<sup>2</sup> Christensen,<sup>4</sup> Douglas and Haldane,<sup>5</sup> Grollman<sup>6</sup> and Means and Newburgh.<sup>1</sup> To permit better comparison of the values for the circulation rate and oxygen consumption of persons of different sizes, the data of these observers have been recalculated and expressed as liters per square meter per minute and cubic centimeters of oxygen per square meter per minute. Fortunately, the height and weight of all the subjects were given by the respective authors, with the following exceptions. Dr Grollman furnished the data for his subject, which were height, 164 cm, and weight, 63.5 Kg. The values for Boothby's subject were height, 166 cm, and weight, 47.7 Kg. Those for the subject J. H. M. of Means and Newburgh were height, 175 cm, and weight, 73 Kg.

Although the amount of available data is still limited, it seems sufficient to confirm the conclusion of Boothby that there is an essentially linear relationship between the increase in the circulation rate and the increase in the oxygen consumption produced by work. The circulation rate when the subject is at rest under basal conditions (fig. 1) is approximately 2.2 liters per square meter per minute—a figure corresponding to the standard figures given by Grollman as the average obtained for fifty normal subjects. This increases approximately 88 cc for each 100 cc of increase in oxygen consumption per square meter per minute caused by work, as is shown by the heavy straight line in the middle. The two lighter parallel lines have been drawn to indicate that such a line can be only an approximation. The straight

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3 Bock, A. V., Vancaulaert, C., Dill, D. B., Folling, A., and Hurxthal, L. M. Studies in Muscular Activity. III. Dynamical Changes Occurring in Man at Work, *J. Physiol.* **66**: 136 (Oct.) 1928.

4 Christensen, E. H. Beiträge zur Physiologie schwerer körperlicher Arbeit, *Arbeitsphysiol.* **4**: 128, 154, 175 and 499, 1931.

5 Douglas, C. G., and Haldane, J. S. The Regulation of the General Circulation Rate in Man, *J. Physiol.* **56**: 69 (Feb. 14) 1922.

6 Grollman, Arthur. (a) The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, (b) Physiologic Variations in the Cardiac Output of Man. XIII. The Effect of Mild Muscular Exercise on the Cardiac Output, *Am. J. Physiol.* **96**: 8 (Jan.) 1931.

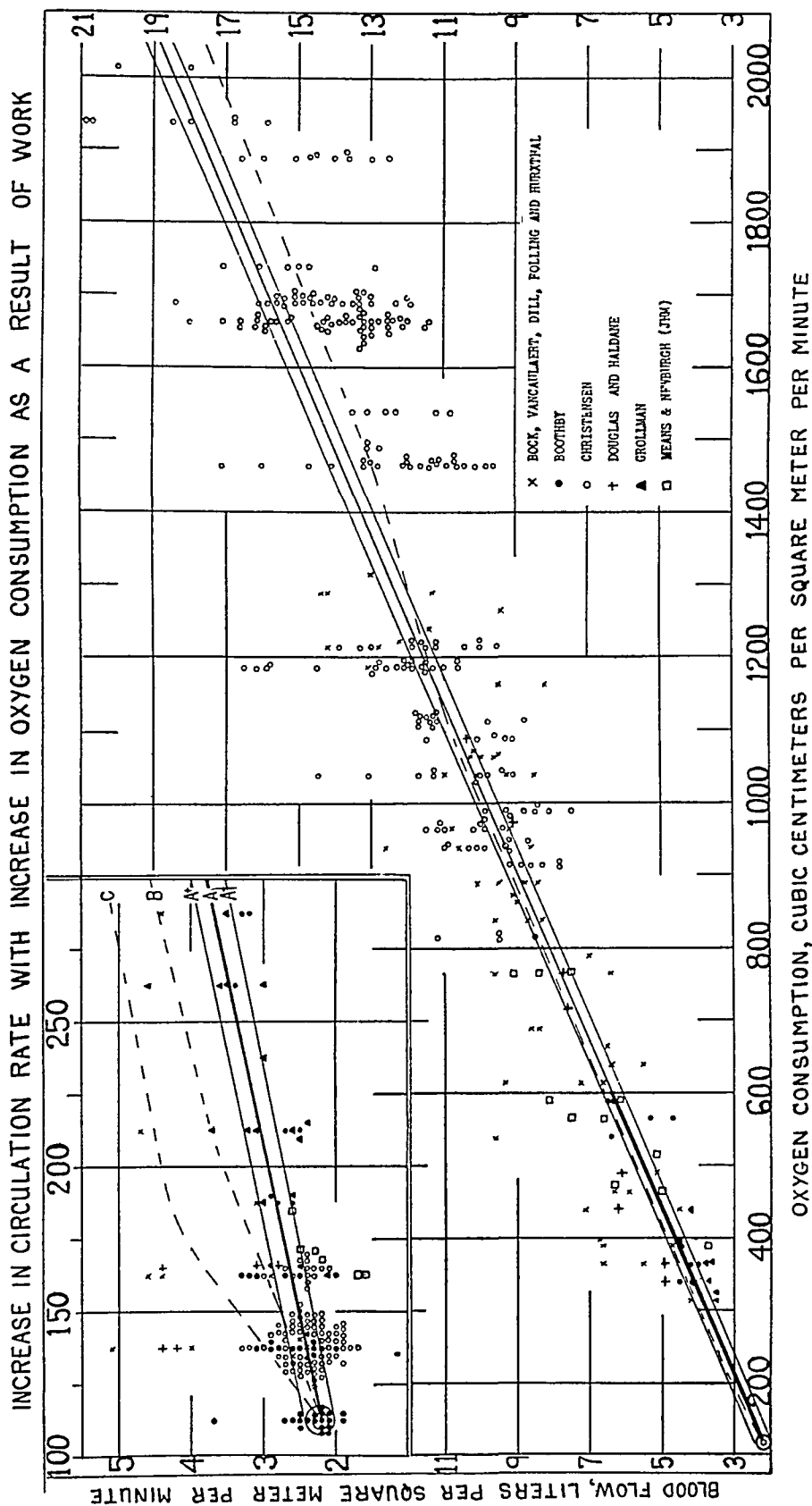


Fig 1—Curves showing the increase in the circulation rate with an increase in oxygen consumption as a result of work. The inserted chart is the enlarged scale for the lower part of the curve *B* indicates the curve for exophthalmic goiter based on studies by Boothby and Fullerton and Harrop, and *C*, the curve for exophthalmic goiter based on studies by Liljestrand and Stenstrom

line as reproduced here is the original one given by Boothby, except that it has been recalculated on the basis of surface area. Although Boothby's graph was based on degrees of work representing an oxygen consumption up to only 600 cc per square meter per minute, it can be extrapolated to extreme degrees of work with little error. It is apparent, however, that this straight line does not exactly represent the entire data. For light work, the data for which are plotted at the lower end of the chart, there is an indication of a slight increase in the circulation rate, which is, however, practically negligibly greater than that indicated by a straight line. On the other hand, with moderately severe work, corresponding to an oxygen consumption of more than 1,200 cc per square meter per minute, there is an indication of slightly better utilization of the carrying power of the blood, which results in a slight, but appreciably slower, rate of increase in the circulation rate. These slight departures from the straight line have been indicated on the chart by the free-hand drawing of an S-shaped curve in a broken line; the data are not large enough or sufficiently homogeneous to justify construction of such a curve by the method of least squares.

Bock and his associates, as well as Douglas and Haldane, determined the circulation rate by equilibration of the carbon dioxide in the lungs with that of the venous blood, whereas the other investigators used either the nitrous oxide method of Krogh and Lindhard or Grollman's modification, using acetylene as the equilibrated gas. Both methods give essentially similar results except at the lower end of the curve, for very light work, where the fallacies inherent in the carbon dioxide method may easily cause proportionately larger errors.

It is of interest to compare the increase in the circulation rate that accompanies the increased oxygen consumption resulting from work by normal subjects with the increase in the circulation rate and oxygen consumption that occurs in persons who have exophthalmic goiter.

Plesch and Davies, Meakins and Long and Bansi showed by other methods that the circulation rate was increased in exophthalmic goiter. In 1915, Liljestrand and Stenstrom,<sup>7</sup> using the nitrous oxide method of Krogh and Lindhard, demonstrated an increase in the circulation rate in exophthalmic goiter; they made seventy observations on eight women and three men. The increase in the circulation rate found by them was surprisingly large, in many instances even exceeding the increase in oxygen consumption, so that the difference in the arterial and venous oxygen was unchanged or even occasionally decreased.

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<sup>7</sup> Liljestrand, G., and Stenstrom, N. Clinical Studies on the Work of the Heart During Rest. I. Blood Flow and Blood Pressure in Exophthalmic Goiter, *Acta med Scandinav* 63: 99, 1925.

Recently, Fullerton and Harrop<sup>8</sup> made a similar study, they used the nitrous oxide method with the simplifications introduced by Grollman<sup>6</sup>. They reported eighty-six determinations on five women and three men, with an average basal metabolic rate of 30.3 per cent above normal and with a circulation rate 41.5 per cent above a normal value of 2.2 liters per square meter per minute. Following the administration of a solution of iodine and thyroidectomy, both the metabolic and the circulation rate returned close to the normal standard figure.

During the last two years we have carried out a series of one hundred and sixty determinations of the circulation rate of seven women and four men who had exophthalmic goiter, in these determinations we used acetylene, as suggested by Grollman, instead of nitrous oxide because it is much more simple to analyze. The results for the basal metabolic rate, oxygen consumption per minute and blood flow in liters per square meter per minute are given in the table, and every determination made on each subject is included. In all experiments on the circulation rate there is quite a spread in the determinations made under apparently identical conditions, even with good technic, and in determinations on patients with exophthalmic goiter this spread is definitely larger than the same observers obtained for normal subjects. Therefore, this increased divergence in exophthalmic goiter cannot necessarily be attributed solely to faulty technic but may represent a greater variability in, or instability of, the circulation rate in this disease, at least, it does not seem safe to us to exclude any of our own observations. Although the variations do not greatly affect the general picture of the average circulation rate in exophthalmic goiter if a sufficient number of determinations are made, the discrepancy in the reported results of determinations in the same case, as can be seen in the tabular presentation of the data, nevertheless precludes the utilization of the method for diagnostic purposes. On the other hand, our data, in conjunction with similar observations reported in the literature, enable one to understand better the effect of the disease on the heart and circulation rates, with the resultant clinical phenomena.

We have plotted, in figure 2, against oxygen consumption per square meter per minute our own results of studies of the circulation rate in liters per square meter per minute made on patients with exophthalmic goiter and, in addition, the observations of Liljestrand and Stenstrom and of Fullerton and Harrop, recalculated on the square meter basis. We have also drawn in the smoothed curve for the increases in the circulation rate due to work, as obtained from figure 1. In order to aid in demonstrating the differences, as well as the similarities, in these

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8 Fullerton, C. W., and Harrop, G. A., Jr. The Cardiac Output in Hyperthyroidism, *Bull. Johns Hopkins Hosp.* **46**: 203, 1930.

*Circulation Rate in Exophthalmic Goiter    Essential Data on Seven Women and  
Four Men*

	Date, 1932	Weight, Kg	Basal Metabolic Rate	Oxygen Consumption, Cc per Sq M per Minute	Blood Flow, Liters per Square Meter per Minute		
					1	2	3
Married woman, age, 48, height, 161 cm	11/19	62.2	+30	268	2.8	3.3	
	11/21	61.6	+31	267	4.0	2.8	
	11/23	61.4	+34	276	2.6	2.9	
	11/24	61.2	+32	272	2.5		
	11/26	61.3	+30	267	3.1		
	11/28	61.6	+39	284	3.1	2.6	
	11/30	60.5	+34	272	2.8	3.1	
	12/ 2	60.5	+32	267	2.2	2.8	
	12/ 3	60.7	+34	272	3.8	3.1	
	12/ 5	60.7	+25	251	3.5	2.6	
	12/ 8	60.7	+26	258	2.6	2.3	
	12/ 9	Thyroidectomy					
	12/22	59.0	+ 2	202	2.3		
	12/27	60.4	- 7	187	2.1	2.2	
Unmarried woman, age, 25, height, 167 cm	9/13	47.2	+46	284	3.7		
	9/24	48.0	+19	229	2.5		
	9/27	Thyroidectomy					
	10/ 6	45.7	+ 1	192	2.7	2.7	
	10/10	46.0	+ 3	198	2.8		
	10/12	46.5	- 2	176	1.9	2.6	
	10/19	46.6	-11	170	2.3		
Unmarried woman, age, 23, height, 159 cm	9/24	53.2	+55	314	3.3	4.3	
	9/27	52.7	+45	295	3.7	3.0	
	9/29	53.1	+38	280	2.9		
	9/30	53.1	+28	259	3.2	3.2	3.2
	10/ 3	54.2	+34	272	3.3	3.1	
	10/ 4	Thyroidectomy					
	10/13	53.4	+13	225	2.8	3.0	
	10/17	54.7	- 1	196	2.1	2.1	
	10/20	55.2	+ 6	214	2.2	2.4	
Man, age, 27, height, 168 cm	1933						
	6/ 8	59.2	+90	440	4.0		
	6/14	57.5	+77	403	3.9		
	6/16	Thyroidectomy					
	6/26	55.0	+15	254	2.8		
	7/ 5	59.8	0	223	2.2		
Man, age, 43, height, 169 cm	1932						
	11/ 8	59.4	+60	360	3.4		
	11/10	60.3	+46	332	4.2	5.0	
	11/11	60.0	+43	325	2.6	4.0	
	11/14	58.9	+26	280	3.3		
	11/16	58.1	+29	293	3.1	3.6	
	11/18	58.1	+28	286	2.5		
	11/18	Thyroidectomy					
	11/26	58.4	+19	266	2.5	2.7	
	11/29	58.2	+ 4	229	2.8	2.4	
Married woman, age, 44, height, 159.5 cm	10/22	64.3	+88	394	4.6		
	10/24	64.7	+70	354	4.0	4.2	
	10/26	63.8	+57	329	3.4	3.2	
	10/28	64.3	+56	321	4.3	4.5	
	10/29	64.2	+51	316	4.1		
	10/31	64.3	+47	305	3.6	4.2	
	11/ 2	63.7	+42	296	3.6	3.0	
	11/ 4	63.5	+39	290	2.7	4.1	
	11/ 7	64.7	+42	291	3.2	4.0	
	11/ 9	64.4	+45	302	3.2	3.0	
	11/10	64.7	+40	289	3.3	3.6	
	11/11	Thyroidectomy					
	11/23	62.8	+13	227	2.5	2.4	
	11/25	63.5	+14	233	4.6	3.9	
	11/28	63.7	+ 4	214	2.6	1.8	

*Circulation Rate in Exophthalmic Goiter    Essential Data on Seven Women and  
Four Men—Continued*

	Date, 1932	Weight, Kg	Basal Metabolic Rate	Oxygen Consumption, Cc per Sq M per Minute	Blood Flow, Liters per Square Meter per Minute		
					1	2	3
Unmarried woman, age, 42, height, 165.5 cm	1933						
	10/ 6	57.8	+42	290	2.3		
	10/12	59.0	+36	284	3.3	2.3	
	10/13	59.0	+30	267	2.6		
	10/16	59.0	+25	258	3.0		
	10/19	60.1	+11	228	1.4		
	10/20	Thyroidectomy					
	10/30	59.5	+ 2	212	2.6		
	11/ 1	59.8	0	208	2.0		
	11/ 6	60.0	- 5	196	2.4	2.1	
	11/ 8	57.9	- 6	191	2.4		
	11/13	57.9	-12	175	2.1		
	Unmarried woman, age, 22, height, 160 cm	9/17	64.6	+74	367	3.9	3.3
9/28		66.3	+49	317	2.6	3.5	
11/ 4		65.6	+68	358	3.7	3.5	
11/ 7		65.7	+52	325	2.7		
11/10		Thyroidectomy					
11/22		66.5	+24	261	2.4	2.2	
Man, age, 32, height, 177.5 cm		1934					
	3/19	53.5	+27	286	3.4	2.2	
	3/21	54.0	+22	274	3.3	2.5	
	3/23	54.4	+13	256	3.3	2.7	
	3/26	55.1	+18	272	3.2	2.4	
	3/28	55.2	+17	268	2.4		
	3/29	Thyroidectomy					
	4/ 9	56.0	- 7	216	2.6		
	4/11	56.0	-12	199	2.6		
	Man, age, 47, height, 177 cm	1932					
11/ 1		75.4	+45	370	2.5		
11/ 4		75.0	+44	362	3.7		
11/ 5		74.3	+45	368	2.4	2.8	
11/ 7		74.4	+37	348	3.2	2.3	
11/ 8		74.0	+31	333	3.0	2.4	
11/ 9		74.1	+27	320	2.5	2.9	
11/11		74.7	+21	304	3.0		
11/11		Thyroidectomy					
11/19		72.3	+ 5	268	2.0	2.7	
11/22		73.6	- 3	242	2.3	2.0	
1933							
1/31		82.2	-27	196	3.7	2.5	
2/14		84.1	-17	216	1.9	2.7	
Married woman, age, 48, height, 159 cm		1932					
	9/14	55.8	+39	274	3.0		
	9/16	55.5	+41	280	3.1	3.4	
	9/19	54.4	+31	258	3.3	2.9	
	9/20	54.7	+32	260	4.5	3.4	3.5
	9/21	54.9	+32	260	3.0	3.4	
	9/22	55.0	+20	234	2.5		
	9/23	55.5	+31	263	3.3	3.5	
	9/26	55.9	+23	247	2.6	3.0	
	9/27	Thyroidectomy					
	10/12	55.3	- 1	195	2.3	2.6	
	10/14	55.5	0	198	2.2	2.2	
	10/17	56.8	- 4	193	2.2		

curves for both work and exophthalmic goiter, we have drawn in on the enlarged section of the work scale in figure 1 for the range of work comparable to the increases in oxygen consumption in exophthalmic goiter the curves for exophthalmic goiter obtained in figure 2

A study of figure 2 shows the following interesting points 1 There is a marked increase in the circulation rate with increasing oxygen consumption in exophthalmic goiter, as is shown by individual observations in all three series of experiments, which is definitely much greater than that which occurs in normal subjects as a result of work, this is indicated by the fact that nearly all the individual observations lie above the mean curve for work 2 The average value for the circulation rate with increasing oxygen consumption in exophthalmic goiter, as found by us, agrees closely with the average value found by Fullerton and Harrop Although our individual determinations show a slightly greater spread than theirs, the mean values of both series are in such close agreement that we have combined these two sets of data to form the group of mean values shown in the upper part of figure 2 3 The means for the group of the observations made by Liljestrand and Stenstrom, as shown clearly in the upper half of figure 2, indicate a much more rapid and a greater increase in the circulation rate for a given increase in oxygen consumption than do the means for the group of our own data combined with those of Fullerton and Harrop Curves have been drawn in on the upper half of figure 2 to represent the general increase in the circulation rate with the increase in the metabolic rate, as measured by an increase in oxygen consumption, for both the Swedish series and the combined American series In addition, the curve representing the increase in the circulation rate of normal persons accompanying increased oxygen consumption resulting from work is again reproduced to aid in differentiating the responses by the circulation in the two conditions

As all three series of the observations on exophthalmic goiter which have just been referred to were made in well equipped laboratories and by observers with considerable experience in experiments of this type, the general accuracy of the three series cannot be questioned, least of all those of Liljestrand and Stenstrom of the Karolinska Institute of Stockholm

What, then, can explain the average agreement of our results with those of Fullerton and Harrop and the markedly greater increase in the circulation rate found by Liljestrand and Stenstrom? First, we think that there is no question that there is a progressive increase in the circulation rate in exophthalmic goiter corresponding to the severity of the disease, as measured by an increase in oxygen consumption Second, this increase in the circulation rate is greater than that which occurs among normal subjects as the result of a corresponding increase

THE INCREASE IN CIRCULATION RATE PRODUCED BY EXOPHTHALMIC GOITER COMPARED WITH THAT PRODUCED IN NORMAL SUBJECTS BY WORK

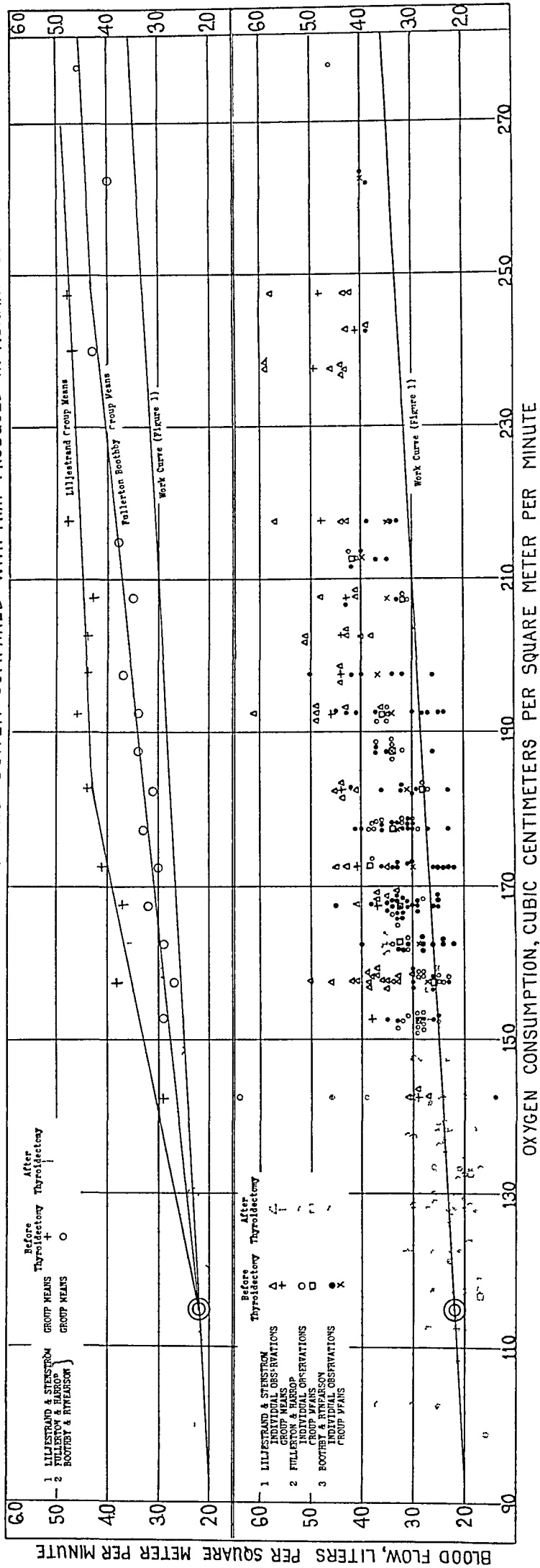


Fig 2—Curves showing the increase in the circulation rate produced by exophthalmic goiter, compared with that produced in normal subjects by work. The values are plotted about the mean curve for the increase in the circulation rate, due to work, taken from figure 1. The upper chart shows the curves for the mean values for the two groups considered, which fall above the mean curve for the increase in the circulation rate due to work.



in oxygen consumption due to work Third, all the patients in our series, as well as all but one patient in Fullerton and Harrop's series, received compound solution of iodine U S P, usually before even the first determination was made On the other hand, the patients observed by Liljestrand and Stenstrom did not receive iodine in any form It is now well recognized that the administration of iodine usually decreases the basal metabolic rate and, at the same time, markedly quiets the forcible and tumultuous beating of the heart Often the powerful action of the heart of the patient with exophthalmic goiter before the administration of iodine is so violent as to shake the bed, usually a definite capillary pulse can be seen in the finger-nails, and this is frequently accompanied by secondary manifestations of cardiac fatigue All these manifestations usually decrease markedly after effective medication with iodine, as do also the typical nervous manifestations of the disease Therefore, we believe that the greater increase in the circulation rate observed by Liljestrand and Stenstrom, as compared with the observations in the other two series, represents a true difference and is the result of an abnormal increase in the circulation rate relative to the increase in oxygen consumption of patients with exophthalmic goiter who do not receive iodine Iodine, therefore, not only tends to decrease the rate of heat production in exophthalmic goiter but also decreases the excessive circulation rate of the patient with the typical, severe form of the disease who has not been treated previously with iodine, although it may not decrease it to the level found for the increase in the circulation rate with increased oxygen consumption produced in normal persons by work

In both our series and Fullerton and Harrop's series there are data on a considerable number of observations following thyroidectomy These are also plotted in figure 2 and can be distinguished from those made before thyroidectomy by the fact that dotted symbols are used Nearly all the mean values of the group are seen to lie close to the line of the circulation rate during work, even if the postoperative determinations were made before the oxygen consumption and the circulation rate returned to the normal basal level This indicates that even if, at the time of observation after thyroidectomy, the heat production and the circulation rate have not returned completely to average normal values, nevertheless the discrepancy between the increased circulation rate and the oxygen consumption in exophthalmic goiter, as compared with the increase due to work, has largely disappeared Liljestrand and Stenstrom likewise made a few observations after thyroidectomy, the circulation rates of their patients, however, did not return to the anticipated values Clinically, it is well known that the return to normal, both in the metabolic rate and in the tumultuous action of the heart, is less rapid and on the average less complete immediately following

thyroidectomy in patients who are not under the influence of iodine as compared with those who have had ample and effective treatment with iodine both before and after operation

#### SUMMARY

The circulation rate is increased in exophthalmic goiter. On the average, the greater the intensity of the disease, as measured by oxygen consumption, the greater is the increase in the circulation rate.

The increase in the circulation rate in patients with exophthalmic goiter who are not treated with iodine, according to the investigations of Liljestrand and Stenstrom, is much greater than that which occurs in normal persons as the result of an increase in oxygen consumption due to work.

The relative increase in the circulation rate for a given increase in oxygen consumption is definitely less in patients who are treated with iodine than in those who have not received iodine. However, even under these conditions the increase in the circulation rate was, on the average, both in our cases and in those of Fullerton and Harrop, slightly greater than that produced in normal persons by a degree of work that caused a similar increase in oxygen consumption.

These facts suggest the hypothesis that in exophthalmic goiter, especially when the patient is not treated with iodine, there is present in the system a peculiar circulatory stimulant that causes a greater increase of the circulation rate than occurs in a normal subject as the result of a corresponding increase in oxygen consumption due to work. In exophthalmic goiter either this peculiar circulatory stimulant is decreased in amount or its effectiveness is lessened by effective medication with iodine.

# INCIDENCE OF BACTEREMIA IN THE PNEUMONIAS AND ITS RELATION TO MORTALITY

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The recovery of pneumococci from the blood stream during the course of pneumococcic pneumonia may be prima facie evidence that the protective mechanism which prevents or overcomes bacteremia is at least partially in abeyance. Whether recovery or death will be the outcome in pneumococcic pneumonia depends to a great extent on whether the protective mechanism alone, or aided by serum, suffices to prevent an increase in the number of organisms or to clear the blood of pneumococci after it has been invaded.

During the past seven and a half years we have regularly taken blood cultures in our study of pneumonia at Harlem Hospital. We have selected for presentation the results of our work during the years between July 1, 1928 and June 30, 1933, because (1) Rosenbluth<sup>1</sup> has already presented our material with respect to bacteremia during the first two years, and (2) during this later five year period we have been able to study the newer types of pneumococci, as segregated and numbered by Georgia Cooper. Not only have we subdivided the cases formerly classed as group IV (originally termed by us the miscellaneous or "x" group), but we have also separated from the organisms elsewhere and formerly included by us as the pneumococcus type II, the subtype IIa of Avery, designated in the classification of Cooper as type V, and the Thomas strain of Sugg, Gaspari, Fleming and Neill, formerly included in type III and now designated type VIII.

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From the Littauer Pneumonia Research Fund of New York University and the Medical Service, Harlem Hospital (Department of Hospitals)

1 Rosenbluth, M B. Relation of Bacteremia in Lobar Pneumonia to Prognosis and Therapy, J A M A 90 1357 (April 28) 1928

In most cases, positive blood cultures give unequivocal evidence of the type of pneumococcus responsible for the illness, and the disappearance of bacteremia in response to treatment may be a real measure of efficient specific therapy. In cases in which invasion of the blood continues in spite of therapy the illness is almost uniformly fatal. On this account the occurrence of bacteremia is worthy of particular study. We shall present our observations with respect to the occurrence of bacteremia and the mortality in the different types in a series of graphs.

#### PROCEDURE AND CRITERIA

The criteria for the diagnosis of pneumonia and of bacteremia, as used at Harlem Hospital, must first be given if these statistics are to be evaluated properly and compared with others. The clinical diagnosis of pneumonia is based on the history and physical findings, including roentgenography or fluoroscopy and the white blood cell count. If recovery occurs, diagnostic importance is attached to the clinical course and laboratory observations, if death, to the clinical course, autopsy and postmortem cultures. In compiling statistics or at the termination of illness, doubtful cases and those incorrectly diagnosed are removed from the series, but no cases of pneumonia are removed because the patients were moribund or died shortly after admission. The diagnosis of pneumococcic pneumonia depends on recovering a bile-soluble diplococcus from the sputum, pharyngeal or laryngeal culture, lung juice<sup>2</sup> culture as obtained by transpleural aspiration in broth and/or blood culture. Sputum or other cultures are studied directly and by injection into mice. The typing is by a specific capsule-swelling reaction with serum of immune rabbits (Neufeld) or by the stained slide technic (Sabin)<sup>3</sup> of agglutination of peritoneal exudate. The organism responsible for septicemia in the mouse is studied in a culture of the heart blood and in a culture from the brain tissue of the mouse.

A blood culture is taken on admission in all cases and is repeated (1) if the temperature continues to be high, or falls, and the pulse rate continues to be rapid, (2) if the temperature rises and the pulse rate becomes more rapid, and (3) if there is a marked change in the condition of the patient. Three cubic centimeters of blood is drawn, of this 1 cc is cultured in 50 cc of broth ( $p_H$  from 7.4 to 7.6, previously tested for growing the pneumococcus well), and 1 cc is cultured in each of two plain agar plates. The blood is expelled into the Petri dish, the melted agar (temperature 41 C.) poured and the whole mixed. Cultures are made post mortem (usually within a half hour) from consolidated lung tissue, from blood from the heart and frequently from the cerebrospinal fluid.

Alternate patients with pneumonia receive probative serum—two doses (5 and 10 cc) of duovalent type I and type II serum, with from 1,500 to 2,500 units of each type per cubic centimeter. In all cases of type I the patients received serum unless in collapse and moribund or in a postcritical condition with agglutinins for type I (slide technic) present in the blood. In all cases of type II in which probative serum has been given the patients continue to receive duovalent serum. In other type II cases the patient receives serum if he has been admitted after a

2 The term lung juice was used to describe the material obtained by trans-thoracic aspiration of the lung. Its constituents are tissue, blood, lymph and exudate, if any.

3 Sabin, A. B. Proc. Soc. Exper. Biol. & Med. 26:492, 1929.

nonserum-treated patient with a type II infection. In other types, serum is given in alternate cases of the type involved, if serum for the type is available.

Pneumonia is regarded as not due to a pneumococcus if there is failure to obtain pneumococci on careful, repeated examinations of the sputum, lung juice and blood, or if another etiologic agent is found. If pneumococci fail to grow in the blood during life, or soon after death, the case is counted as nonbacteremic. The recovered pneumococcus is regarded as causally related to the pneumonia (1) when pneumococcus is found in good sputum or in laryngeal or pharyngeal mucus on a swab, (2) when the pneumococcus is present in lung juice obtained by suction of the lung, (3) when the pneumococcus grows in a blood culture, and (4) when agglutination, previously absent, develops in the blood for the type of pneumococcus recovered in the discharges.

#### DISTRIBUTION OF TYPES

In their classic studies published in 1917, as monograph 7 of the Rockefeller Institute, Avery, Chickering, Cole and Dochez found only 20 per cent of cases of pneumonia in their group or type IV. Cole, in Nelson "Loose-Leaf Medicine," subsequently reported a slightly larger number of cases in this group. Cecil, at Bellevue Hospital, and also Blake, in New Haven, classified 34 and 35 per cent of their cases as belonging in group IV.

In the past five years, only 41 per cent of our cases were of types I, II and III, the remaining 59 per cent included (1) types IV to XXXII (Cooper), (2) our present type x and (3) multiple infections. Our percentage of cases of types I, II and III was even lower than that in the report of Rosenbluth,<sup>1</sup> which embodied the first two years of our experience.

A comparison of our present statistics with those of Rosenbluth disclosed a reduction of pneumococcus type I cases in our series which we do not attempt to explain. We found a decline in the incidence of bacteremia in type I cases from 35 to 27.4 per cent, this is probably due to earlier and more frequent administration of serum. There is also a reduction of the type II and type III cases, but there is an increased incidence of their bacteremias. In type II, the number of cases fell from 19 to 9.4 per cent, and the cases of bacteremia increased from 31 to 38.6 per cent. In type III, the relative number of cases fell from 13.2 to 8.9 per cent, and the bacteremic incidence increased from 25 to 29.6 per cent. In the type II cases, the reduction may be explained by the exclusion of the subtype IIa of Avery as type V, and in the case of type III, the segregation from type III of the cases due to the Thomas strain of Sugg and his co-workers, as type VIII.

#### THE DECLINE OF GROUP X (UNDESIGNATED TYPES)

The comparatively large number of cases now included in the newer types of Cooper and in the smaller x group and the increased bacteremic incidence in this section make it worth while to analyze these cases.

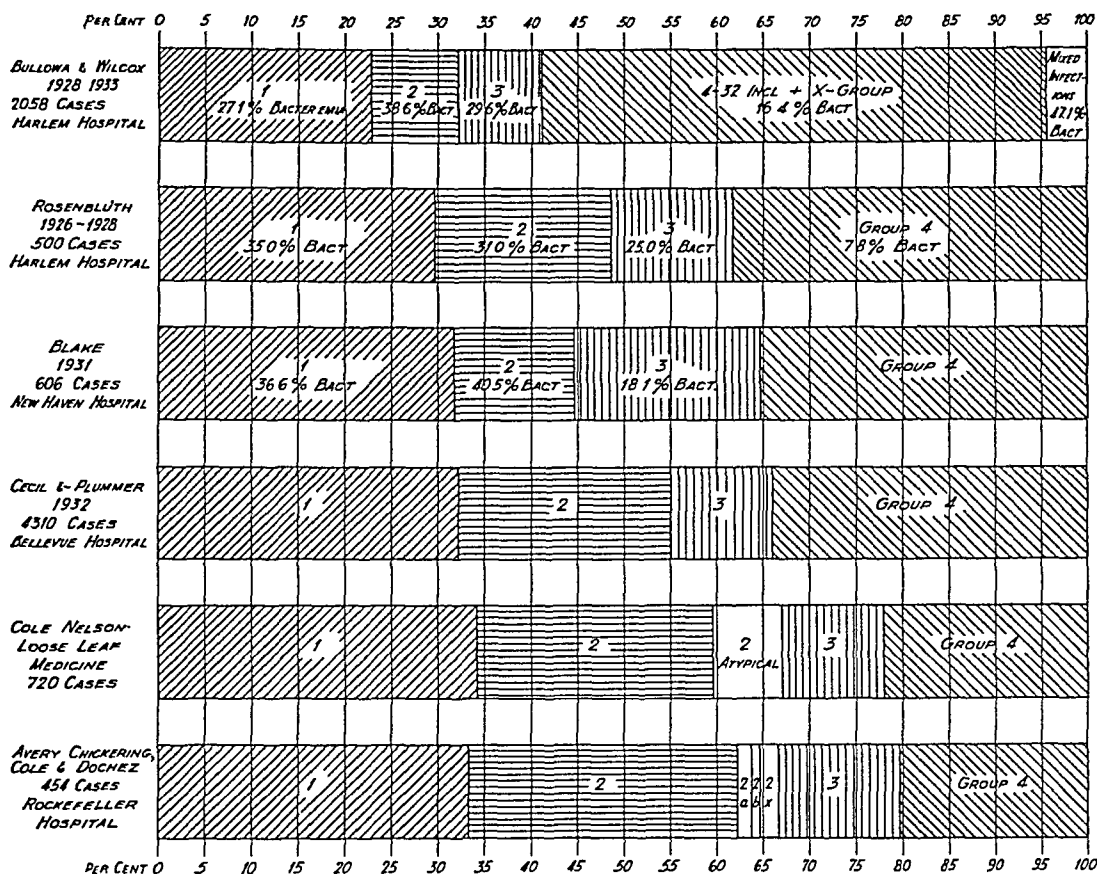


Chart 1—Comparison of the distribution of types of pneumococcic pneumonia and of bacteremia in each reported study

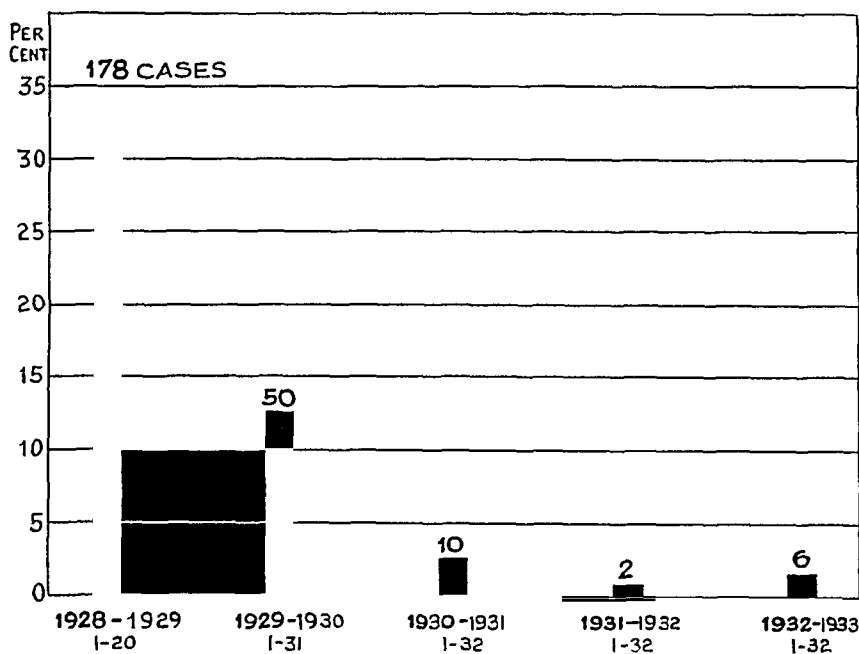


Chart 2—Decline of the x group in 2,058 cases of adult pneumococcic pneumonia. Each block indicates the percentage of cases unclassified in one year. The figures under the year reveal the number of types for which typing was done in that year. Above each block is the number of unclassified or x group cases each year.

further. In our series, the number of cases of bacteremia in what was formerly called group x was 16.5 per cent, in Rosenbluth's, it was 7.8 per cent.

In the last five years the x group has diminished, so that it now comprises only 3 per cent of our cases annually. In the first year of these studies, 1928-1929, we were typing to type XX (Cooper), that year there were one hundred and seventy-eight cases in the x group. During the past year there were only six cases which did not fall into the thirty-two Cooper types, and in the previous year, two cases. Still more interesting has been the course of the frequency of invasion of

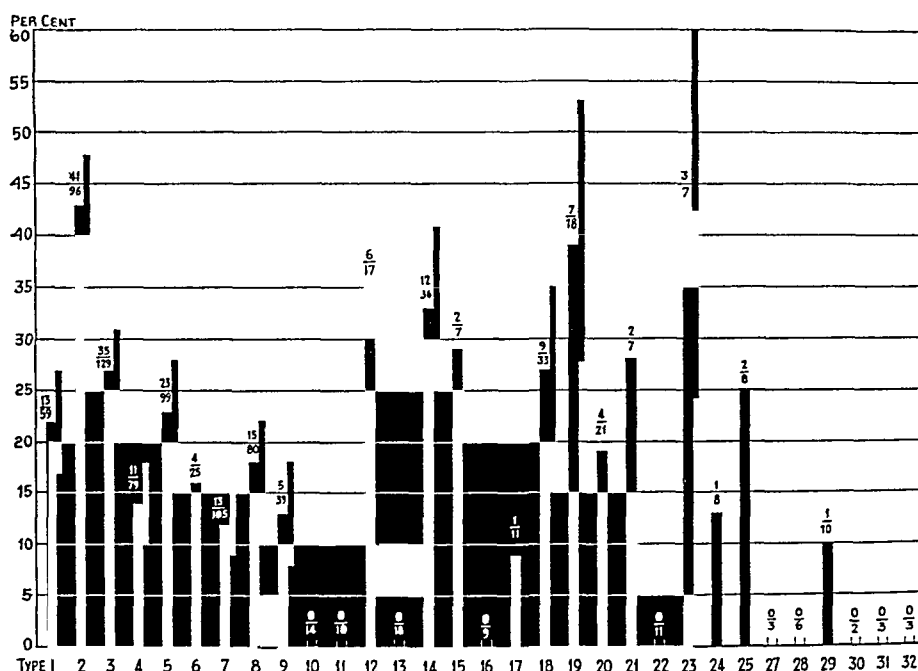


Chart 3—Incidence of cases of bacteremia in which no serum was given, numerically arranged. The standard error is indicated as a bayonet in types in which 18 or more cases were observed. The standard error is given in the text for types in which there were fewer than 18 cases. The standard error is calculated as  $E = \sqrt{\frac{pq}{n}}$  when E equals the standard error, p, the rate of bacteremia invasion, q, 1—p, and n, the number of cases observed. The numerator of each fraction indicates the number of bacteremic cases, the denominator the total number of cases.

the blood. In 1928-1929 there were eleven cases of invasion by unclassified organisms, in 1929-1930 there were two, in 1930-1931, one, in 1931-1932, none, and in 1932-1933, none. In the entire five year period there were four hundred and twenty-seven cases of bacteremia. Fifteen, or 3.5 per cent, were not typed. This decline in the unclassified cases has been experienced wherever similar studies have been made.

INVASION OF THE BLOOD IN CASES FORMERLY IN GROUP IV  
("X" OR MISCELLANEOUS)

There is much misinformation concerning the virulence of cases formerly included in group IV. We have prepared a graph (chart 3)

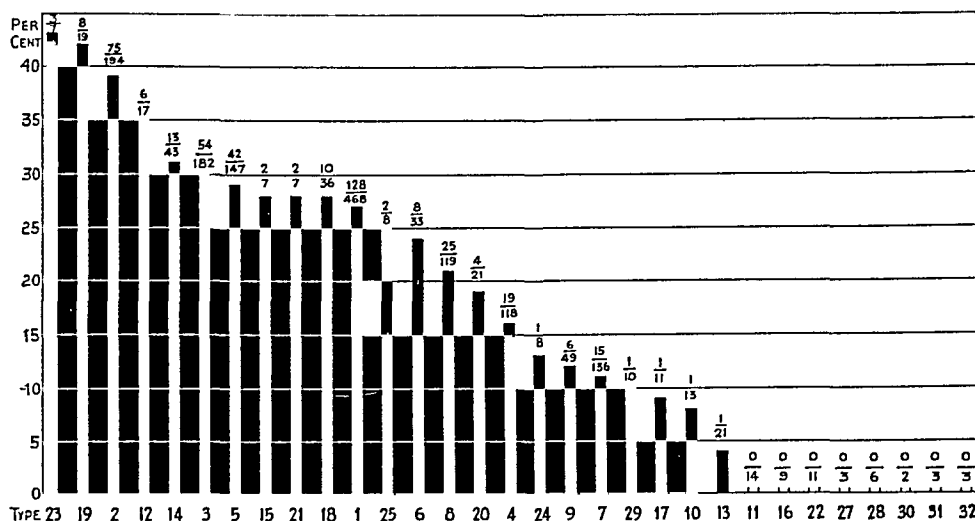


Chart 4—Incidence of bacteremia in the order of percentage frequency of cases of bacteremia in pneumonia of each type. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

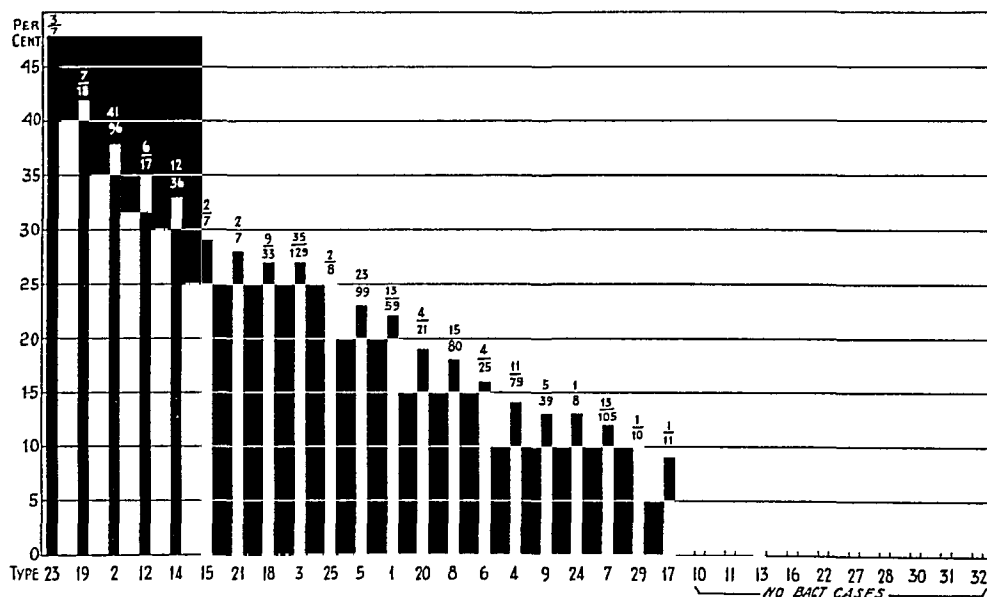


Chart 5—Incidence of bacteremia in the order of percentage frequency of cases of bacteremia in pneumonias of each type. Only cases in which no serum was given are included. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

in which the bacteremic incidence for each type is given. A glance shows that the bacteremic incidence varies, and that in some the incidence is greater than the incidence in types I, II or III. The standard error



of the observations has been computed and attached as a bayonet to the top of the blocks whenever more than eighteen cases have been observed. In each instance the fraction above the block shows the num-

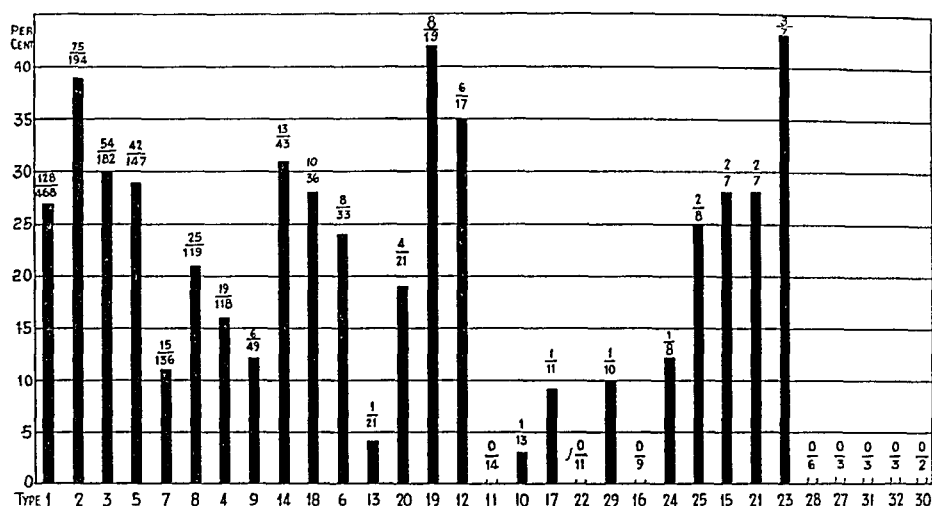


Chart 6—Incidence of bacteremia in the order of numerical frequency of the occurrence of bacteremia in pneumonia of different types. All patients, those treated by serum and those not treated by serum, are included. The numerator indicates the number of bacteremic cases, the denominator the total number of cases.

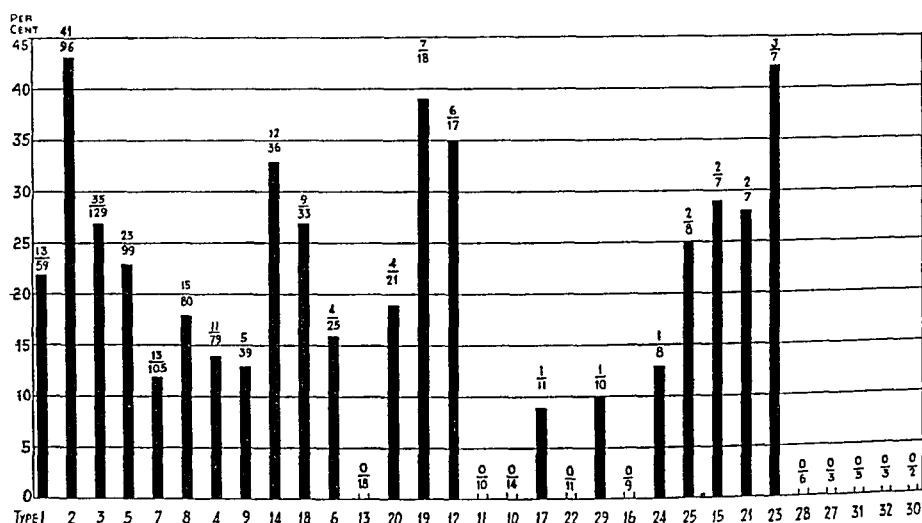


Chart 7—Incidence of bacteremia in the order of numerical frequency of the occurrence of bacteremia in pneumonia of different types. Only cases in which no serum was given are included. The numerator indicates the number of bacteremic cases and the denominator the total number of cases.

ber of bacteremic cases as numerator and the total number of cases of the type as denominator. In some types, bacteria have not as yet been recovered by us from the blood stream of a patient. For types with

fewer than eighteen observed cases the standard error is as shown in the table. It should be emphasized also that in cases in which no bacteremia has been observed as yet, the standard error may be very large, especially when there are few cases.

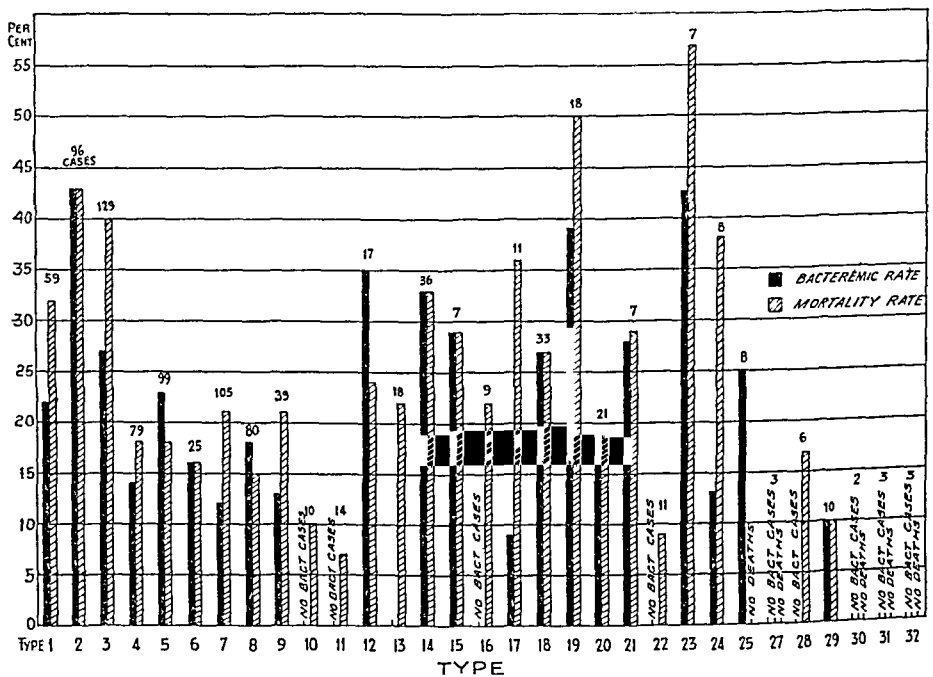
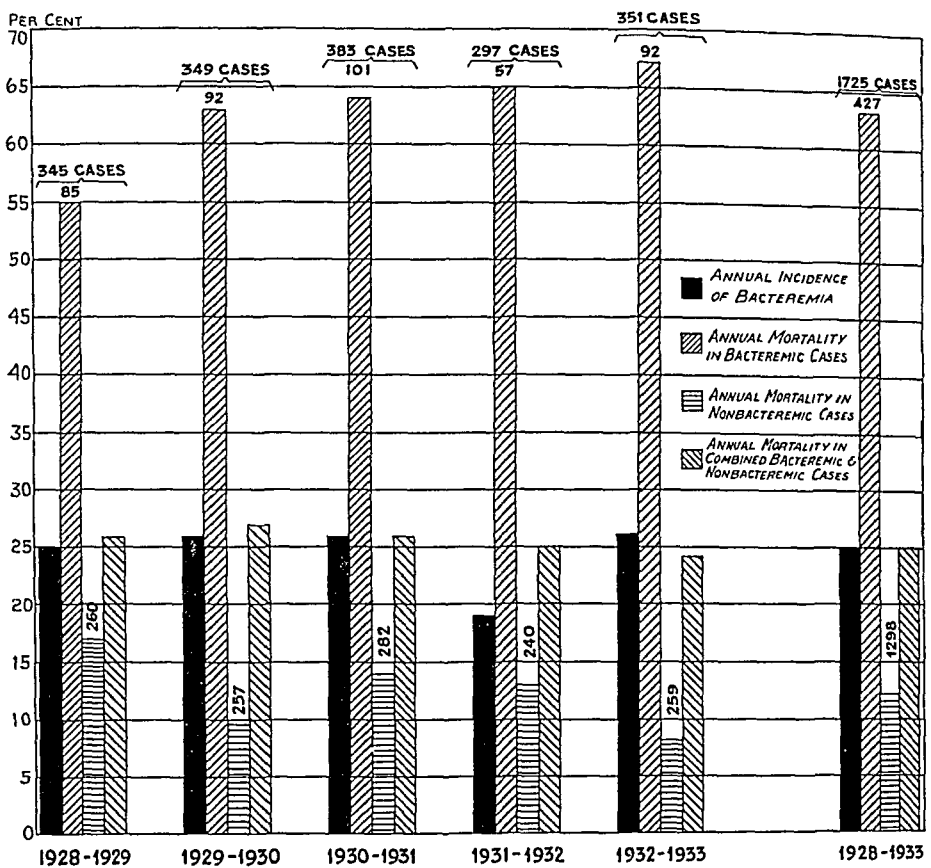
Chart 3 shows that type V, formerly included in type II, is less invasive than type II, and that type VIII is less invasive than type III, with which it was formerly combined. Of all the types which do invade the blood, type XXIII is apparently most invasive, with 42.8 per cent. Some of the types most frequently encountered have a lower bacteremic incidence than those which appear infrequently. The infrequently encountered diseases may be more fatal when they occur. Accordingly, it is important to have available specific serum for the infrequent, but fatal, types.

*Standard Error for Types with Fewer than Eighteen Cases*

Type	Bacteremia, per Cent	Standard Error per Cent
VI	16.0	7.3
XII	35.0	11.0
XV	28.5	17.0
XVII	9.0	8.6
XX	19.0	8.7
XXI	28.0	17.0
XXIV	12.5	20.0
XXV	25.0	15.0
XXIX	10.0	3.0

To judge the importance of each type of pneumococcus as a cause of bacteremia, the types are arranged in the order of percentile frequency of occurrence of cases of bacteremia in charts 4 and 5, and in charts 6 and 7, in the order of frequency in which the pneumococci are encountered in the blood. Charts 4 and 6 give all cases and charts 5 and 7 only cases in which no serum was given.

Although less invasive than at least ten other types of pneumococci, the type I pneumococcus is the organism most frequently encountered in the blood stream of patients suffering from pneumococcic pneumonia. Type II is the second most frequently encountered organism in the blood of patients with pneumococcic pneumonia. Although it invades the blood of more than 40 per cent of its victims, in percentage incidence of bacteremia it is only third among the thirty-two types. Types XXIII and XIX invade the blood more frequently than type II. Type III, though ranking third in the order of frequency in the number of cases encountered, is ninth in the order of percentage occurrence of bacteremia.



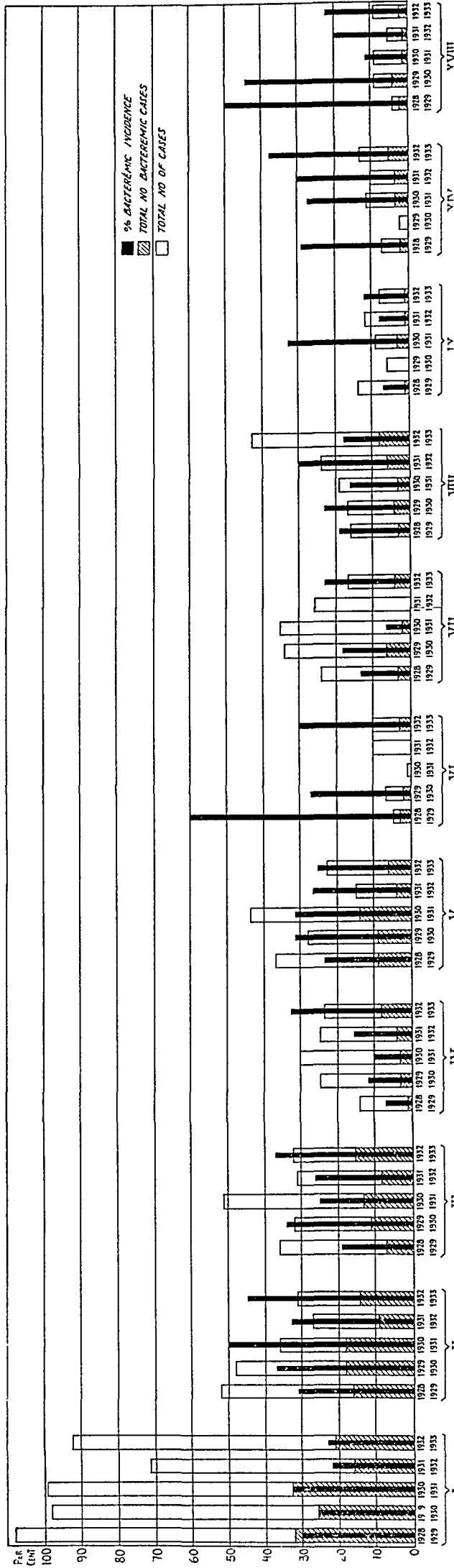


Chart 10—Annual variation of bacteremic incidence in types occurring frequently in adult pneumococcal pneumonia The clear block indicates the number of cases in each year, the superimposed cross-hatching indicates the number of cases of bacteremia, the black block indicates the bacteremic incidence per hundred cases, and the space between the horizontal lines denotes 10 cases and also 10 per cent

## MORTALITY RATE

In a recent article, Cecil and Plummer<sup>4</sup> called attention to the fact that in the case of type II the percentage of bacteremic incidence and the percentage of mortality approached each other. In our study of seventeen hundred and twenty-five cases of pneumococcic pneumonia of definite type due to a single pneumococcus, encountered during the last five years, it appeared that the bacteremic incidence and the rate of group fatality in pneumococcic pneumonias as a group were approxi-

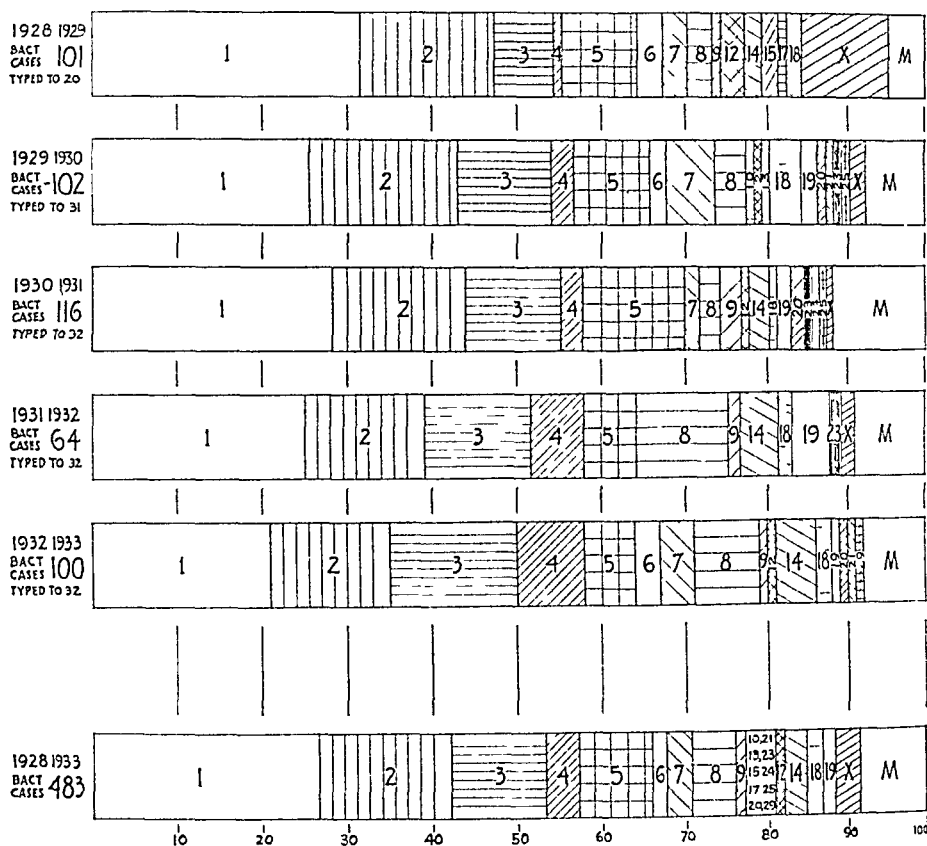


Chart 11—Annual relative distribution of bacteremia according to each type of pneumococcus among 2,058 cases of pneumococcic pneumonia. *M* indicates a multiple infection.

mately the same (chart 8), i. e., 25 per cent, with the exception of one year (1931-1932) when the bacteremic incidence was lower than the mortality rate. In that year the bacteremic incidence was 18 per cent while the mortality rate was 25 per cent.

A glance at chart 8 will show, however, that from year to year there was a steady though slight increase in the mortality of bacteremic cases. This may be due to the increasing number of cases for which

<sup>4</sup> Cecil Russell L., and Plummer Norman. Pneumococcus Type II Pneumonia, *I A M A* 98 779 (March 15) 1932.

we have as yet no serum and, accordingly, no means of direct therapeutic attack

The death rate in the bacteremic and in the nonbacteremic cases is very different, and is shown in chart 8. In general, the bacteremic mortality is two or more times greater than in the nonbacteremic cases

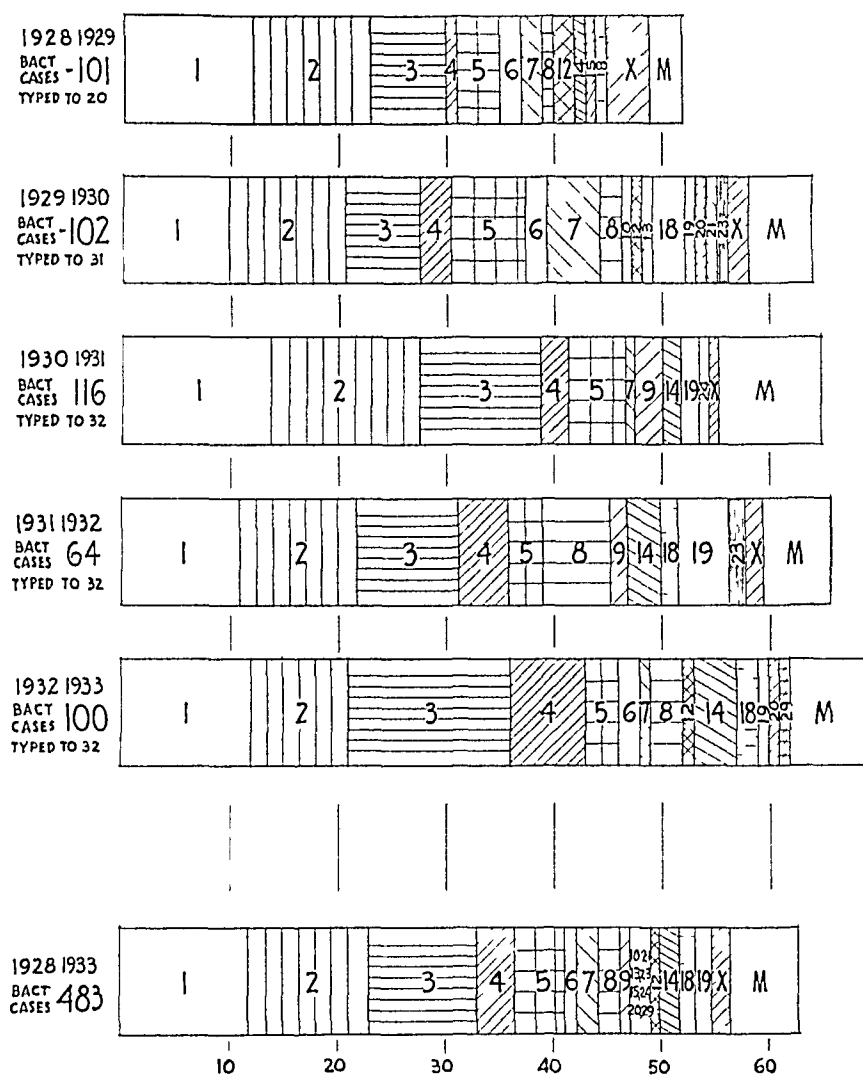


Chart 12—Annual relative distribution of fatal cases of bacteremia due to various types of pneumococci among 2,058 cases of pneumococcic pneumonia. *M* indicates a multiple infection.

Patients infected with different pneumococcic types react so differently that it seemed well to study the mortality in the different types separately.

Interesting facts were revealed when the types we studied were separated with respect to their behavior as to bacteremia and mortality, as is done in chart 9. In many cases the percentage of bacteremia and mortality are the same, though the percentage of mortality ranges from 10 to 43. This is especially well shown in types II, VI, XIV, XV,

XVIII, XX, XXI and XXIX On the other hand, in some instances, notably in type I, the bacteremic incidence is less than the mortality. This also occurs in types III, IV, VII, IX, XVII, XIX, XXIII and XXIV There are other types in which the bacteremic incidence is greater than the fatality rate, as in types V, VIII and XII There are some types, however, in which there were fatal cases but no bacteremia,

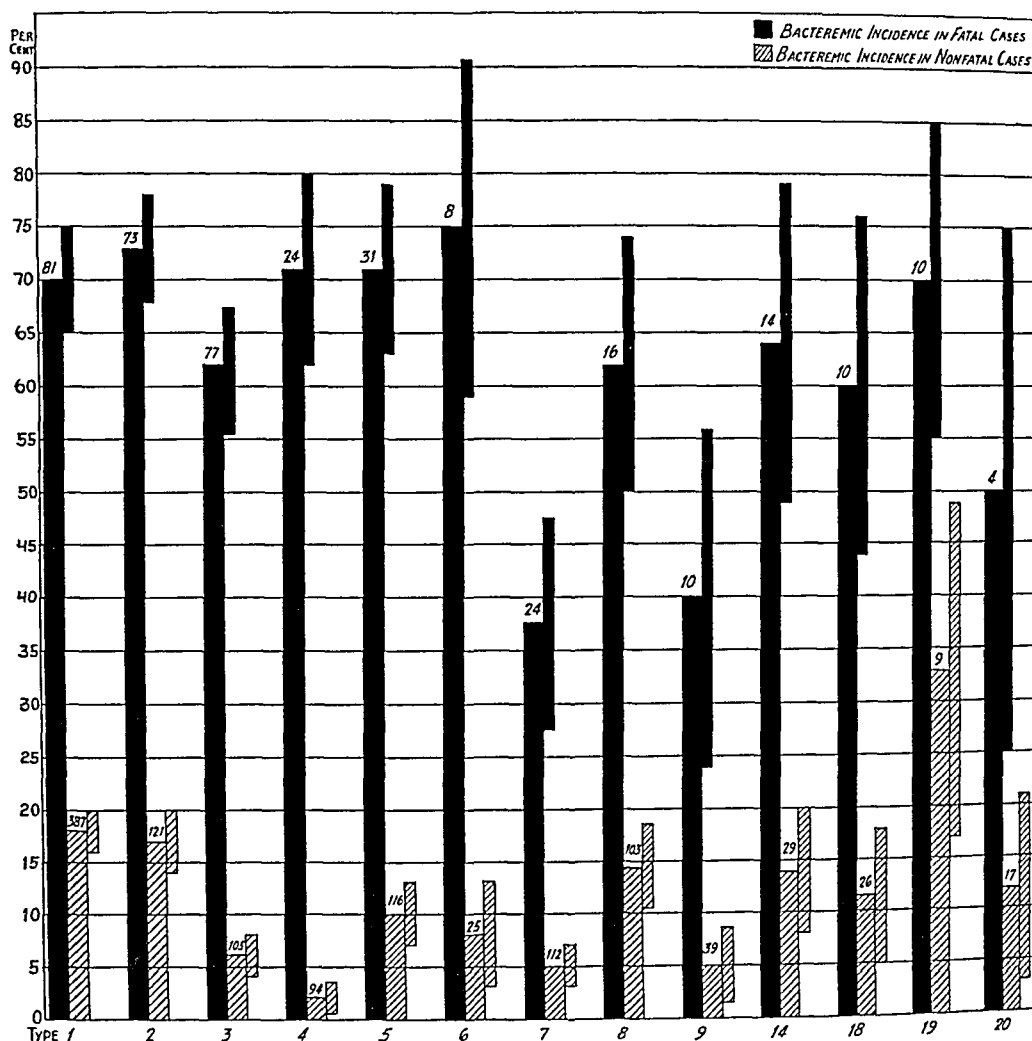


Chart 13—Incidence of bacteremia in fatal (black) and nonfatal (cross-hatched) cases among thirteen of the most important types of pneumococcal pneumonia occurring in 1,725 cases due to a single type of organism. Note the relative infrequency of bacteremia in the nonfatal cases. The number of cases involved is given above each block. The bayonet indicates the standard error of the observation. Calculation of the standard error is indicated in the legend for figure 3.

as in X, XI, XVI, XXII and XXVIII, and there was one—type XXV—in which there was invasion of the blood in two of the eight cases, with recovery in all eight.

## ANNUAL VARIATION IN BACTEREMIC INCIDENCE

In order to determine whether the incidence of bacteremia was constant or varied from year to year, a study of the annual incidence was made. In chart 10 the total bacteremic incidence for a number of frequent types is separated into the constituent years. The percentage of bacteremia is indicated against a cross-hatched block, which shows the number of cases in which the blood was invaded, and a clear block, which shows the number of cases during the year. The decline in the type I cases from year to year is striking. A decline occurred in the bacteremic cases with the exception of one year. The decrease in the percentage of bacteremia from 30 to 21 per cent in the last two years may have been brought about to a varying extent by (1) the larger unitage of serum employed as probative serum, and (2) improvements in our typing practice, as well as (3) the introduction of typing from the lung juice, with consequent earlier treatment in some cases.

An increase seems to have occurred in the percentage of invasions of the blood among type II cases, though the total number of cases diminished. In type III, though the number of cases has been approximately the same in each year, there seems to be an upward trend in the bacteremia. In type IV the number of cases of bacteremia has steadily increased. In type V the percentage of cases of bacteremia at first increased and then decreased. Two bacteremic cases were observed in type VI in the first year of our study. In the second year they were fewer, and for two years there were no cases of invasion of the blood. Last year bacteremia occurred in four of the ten cases. In type VII the percentage of invasions of the blood increased and then diminished, though the number of cases diminished. One year there were no cases of invasions of the blood. The number of type VIII cases seems to be steadily increasing, and there is an increase in the percentage of bacteremia. In type IX there have been few cases, too few to study the trend. In type XIV the number of cases of bacteremia has increased, without significant changes in the number of cases. In type XVIII, though the cases have been few, the bacteremic incidence seems to have diminished.

No one can tell what studies such as these will reveal when they have been continued over a sufficient period. We may learn much of the epidemic variation of the different types. Possibly we shall learn to be forearmed with serum for approaching increased incidence, or with vaccine as a preventive to ward off needless illness and death. There may be cycles in these diseases caused by the different types, just as there are in scarlet fever and measles.



## DISTRIBUTION OF BACTEREMIA AND FATALITIES

It seemed important to contrast the annual relative distribution of bacteremia and the deaths in bacteremic cases, with a view to determining whether there was marked variation in each type and from year to year. Accordingly, graphs 11 and 12 were prepared. Our study revealed that types I, II and III make up slightly more than 50 per cent of all the cases. Types I and II contribute between 30 and 40 per cent.

The importance and the variation of the other types is revealed. Type IV which, in the first year of our study, was responsible for only 2 per cent of the bacteremic cases, was responsible for 7.5 per cent in the last year. Type V became more important and then less. Type VIII gradually acquired greater importance. The number of multiple infections has varied from year to year. It was greatest (12 per cent) in the season of 1930-1931 when infection by *Streptococcus haemolyticus* was prevalent. The x group has disappeared as a cause of bacteremia in our series.

It is evident that type II, in spite of the separation of type V, has remained important as a cause of bacteremia, while type III has increased, though its relative importance as a cause of pneumonia, as shown in chart 1, has diminished.

On examining the relative distribution of deaths in the bacteremic cases for each type (chart 12), it will be found that in the bacteremic cases 64 per cent of the patients died, and that though 50 per cent of the bacteremic cases were caused by types I, II and III, only 33 per cent of the deaths were caused by the three types. This change from what was to be expected has been accomplished by the use of serum for types I and II.

Though the bacteremia in type II cases did not decline in incidence, the cases were relatively fewer. The portion of the death rate due to this type among the cases of bacteremia was diminished in the last year of our study and the bacteremic fatality from this type became 8 per cent, whereas 12 or 13 per cent of the cases of bacteremia were due to this type.

The chart further reveals that an increasing percentage of the deaths in the bacteremic cases is due to the increasing number of deaths due to type III and the types of higher number described by Cooper. For these cases, serums or other direct treatment should be made available, if possible.

From what has already been said there can be no doubt that the occurrence of bacteremia is an event which exerts a marked influence on the outcome of pneumococcal pneumonia. We have accordingly shown in chart 13, thirteen of the most frequent types, and have indicated the bacteremic incidence in fatal and in nonfatal cases. Above

each block is placed the number of cases observed. We have indicated by the bayonet attached in each case the standard error of the specimen.

It is readily seen that the incidence of bacteremia in the fatal cases and in the nonfatal cases varies in the different types, and that invasion of the blood may be assigned less influence in producing death in some types than in others.

Types III and IV had a high bacteremic incidence among fatal cases and a relatively low one among those with recovery. Types VII and IX had a low bacteremic incidence in both fatal and nonfatal cases. In type XIX both in fatal cases and in cases with recovery, there were frequent invasions of the blood stream.

#### SUMMARY

1. The incidence of bacteremia in connection with the fatality rate is listed for different types of pneumococcic pneumonia in a series of seventeen hundred and twenty-five cases due to a single type, occurring over a five year period, at Harlem Hospital.

2. The percentage of invasion of the blood differs for the different types, though in the main the percentages of invasiveness and mortality are approximately the same.

3. The importance of (1) differentiating the types formerly included as group IV or the x group and (2) of typing individual cases for prognosis and eventual treatment when specific treatment is available is manifest.

4. Only 3 per cent of pneumococcic pneumonias escape classification at the present time when typing is carried from I to XXXII (Cooper).

5. The variation in percentage of invasion and fatality from year to year in different pneumococcic types is evidence of the variations which are encountered from season to season, and shows the necessity of extending over several years the testing of any proposed curative substance.

# LEUKEMIC SINUS RETICULOSIS (MONOCYTIC LEUKEMIA) WITH INTESTINAL OBSTRUCTION

REPORT OF A CASE WITH PARTIAL AUTOPSY

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Thirty years ago acute leukemia was regarded as a disease of but one type—lymphatic leukemia. Gradually myelogenous acute leukemia came to be recognized, which seems to occur far more frequently than the lymphatic variety. Today room is being made for a third claimant—monocytic leukemia.

Full acceptance of monocytic leukemia as a clinical and pathologic entity will depend ultimately on indisputable proof of the derivation of the circulating monocytes. Such proof will involve the recognition of a third hematopoietic system, the occasional hyperplasia of which may logically be expected to result in leukemia comparable to myeloid and lymphoid leukemia. Unfortunately, the ancestry of cells, like the ancestry of human beings, is often easy and pleasing to claim but hard to verify. The studies of Maximow,<sup>1</sup> of Kiyono<sup>2</sup> and of Sabin<sup>3</sup> have convinced most investigators that circulating monocytes are derived from some part of the reticulo-endothelial system. Exactly which part and the precise nature of this system are still somewhat obscure.

The first case of monocytic leukemia was reported by Reschad and Schilling-Torgau<sup>4</sup> in 1913. In the subsequent twenty years the new-

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1 Maximow, A. Les relations des cellules sanguines avec le tissu conjonctif et avec l'endothelium, *Ann d'anat path* **4** 701 (July) 1927.

2 Kiyono, K., and Nakanoin, T. Weitere Untersuchungen uber die Histiozyten, *Acta scholae med univ imp in Kioto* **3** 55, 1919.

3 Sabin, F. R. Studies on Living Human Blood Cells, *Bull Johns Hopkins Hosp* **34** 277, 1923. Sabin, F., Doan, C. A., and Cunningham, R. S. Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Contrib Embryol* **16** 125, 1925.

4 Reschad, H., and Schilling-Torgau, V. Ueber eine neue Leukamie durch echte Uebergangsformen (Splenozytenleukamie) und ihre Bedeutung fur die Selbstandigkeit dieser Zellen, *Munchen med Wchnschr* **60** 1981, 1913.

comer to the leukemic field has sometimes been hard put to it for survival. The first few reported cases were dismissed by certain writers as instances of "an ordinary myelogenous leukemia with a one-sided differentiation into monocytes" (Hirschfeld,<sup>5</sup> 1925) or a "temporary variant of myelogenous leukemia" (Naegeli,<sup>6</sup> 1923). In 1927 Piney<sup>7</sup> declared that monocytic leukemia belonged to the group of myeloses, "not being a special form of leucosis (leukemia) dependent upon proliferation of the cells of a third hematopoietic system." However, in 1928 Merklen and Wolf<sup>8</sup> seemed to draw conclusive distinctions for the three types of leukemia, and in 1930 Dameshek<sup>9</sup> assembled eighteen well substantiated cases of acute monocytic leukemia. Recently, Foord, Parsons and Butt<sup>10</sup> (the last two workers being from the laboratory of the Los Angeles County Hospital) compiled an excellent review of the literature and added four cases (two with autopsy and one with biopsy).

#### RETICULO-ENDOTHELIAL SYSTEM

All attempts to define the origin of the phagocytic group of cells, or even to classify the phagocytes as they arrange themselves in various diseases, have been unsatisfactory, and the results probably will require modification as the information becomes more exact. Aschoff seemed to illumine the darkness when he dignified these scattered cells by regarding them collectively as a single organ which he named the reticulo-endothelial system. However, MacCallum<sup>11</sup> expressed the opinion that "Aschoff has cut the knot by merely coining a name—the reticulo-endothelial system—which evades any hard and fast adherence to a theory of origin of the cells since both reticulum cells and endothelium are brought in." MacCallum maintained that the endothelial cells which form the lining of the blood and lymph channels have the one function of lining these channels, and that one indulges one's fancy when one supposes that they ever act as phagocytes or that they divide to form

5 Hirschfeld, H. *Handbuch der Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 1, p. 411.

6 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 4, Berlin, Julius Springer, 1923.

7 Piney, A. *Recent Advances in Hematology*, Philadelphia, P. Blakiston's Son & Co., 1927, p. 47.

8 Merklen, M., and Wolf, M. *Leucémies à monocytes*, *Rev. de méd.*, Paris **45**: 154, 1928.

9 Dameshek, W. *Acute Monocytic (Histiocytic) Leukemia*, *Arch. Int. Med.* **46**: 718 (Oct.) 1930.

10 Foord, A. G., Parsons, L., and Butt, E. M. *Leukemic Reticulo-Endotheliosis (Monocytic Leukemia)*, *J. A. M. A.* **101**: 1859 (Dec. 9) 1933.

11 MacCallum, W. G. *Text-Book of Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1932.

wandering cells of any sort Maximow<sup>12</sup> shared MacCallum's distaste for the term "reticulo-endothelium" as applied to the system of active phagocytic wandering cells. He thought that "the most appropriate name for these cells is histiocytes. Another widely used name, reticulo-endothelium, is not suitable, first, because it refers to only one of the representatives of the system, namely, to the reticular cells, and secondly because it creates the incorrect impression that the endothelium of the common blood vessels also belongs to this system."

The confusion undoubtedly arises from the old difficulty of finding a name the implications of which are restricted to the ascertained facts. The cellular elements in the liver, the spleen, the lymphoid tissues, the bone marrow, the connective tissue, the blood and some of the glands of internal secretion were recognized and grouped into a "system" because of the common ability to store dyes. Phagocytosis is the essential property of the reticulo-endothelial system, and it was on the basis of this common function that the reticulo-endothelial system was described and defined by Aschoff. Unfortunately, the name he gave it has exercised a tyranny on the minds of subsequent writers, some of whom have incautiously assumed that the cells of the reticulo-endothelial system are identical anatomically and genetically as well as functionally. These assumptions rest on uncertain ground. If Aschoff's term is used, it should be remembered that the knowledge of the reticulo-endothelial system is still largely confined to the functional phenomena which he described. The origin and interrelationships of the scavenger cells are not fully understood.

For the sake of formulating some simple concepts of the subject it may be pardonable to mix fact with theory. The "reticulo-endothelial cell" is distinguished chiefly by its powers of phagocytosis, of locomotion and of alteration in size and in activity, in all of which properties it somewhat resembles the ameba. Apparently it may be mobilized by the functional demand, either locally or from many widely separated sources. One sees it at work in the most active form as a macrophage in inflammatory processes. When it is not active it is found at rest chiefly in three locations: (1) in the sinuses of the spleen, the lymph glands, the liver and the bone marrow, (2) in the connective tissues (histiocytes), and (3) in the blood (monocytes). Changes from one type of cell to another have been reported, but there seems irrefutable evidence for only one transformation. The lymphocyte may apparently develop into an active monocyte or into a histiocyte, which in turn may become an inactive fibroblast.

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12 Maximow, A., and Bloom, W. *Text-Book of Histology*, Philadelphia, W. B. Saunders Company, 1930, p. 126.

## THE MONOCYTE

Some authorities maintain that in the adult there are primitive reticular or reticulo-endothelial cells which can develop in any one of three or four directions depending on the stimulus which the cell receives. Of course, if this process becomes irreversible late in the development of the cell, transformations between the less differentiated types of cells seem theoretically possible. However, as has been seen, there is convincing evidence for but one such transformation (from lymphocyte to monocyte, Maximow and Bloom<sup>12</sup>). Members of the triphyletic or polyphyletic school seem to base their opinion on flimsy ground. They assume (in harmony with the monophyletists) a common ancestral cell for all of the leukocytes. They think, however, that at the time of birth these ancestral cells have already been differentiated (probably irreversibly) into hematopoietic tissues, each tissue capable of producing its own specific leukocytic cell (lymphocyte, monocyte or granulocyte).

Amid the conflicting views it seems that the weight of evidence supports the theory of a sharp separation between the monocyte on the one hand and the granulocyte and the lymphocyte on the other. The evidence also indicates an independent origin for monocytic tissue, probably in some part of the reticulo-endothelium.

Gittins and Hawksley<sup>13</sup> in a recent communication suggested that the site of origin of the monocytes may be the lymphatic endothelium. They pointed out that, according to Maximow, lymphocytes are produced not from the lymphatic endothelium but predominantly from older lymphocytes, so that what is seen in lymphatic leukemia is not an endothelial proliferation but an excessive multiplication of formed lymphocytes in the lymph glands. "This granted, it is not surprising that lymphatic endothelial proliferation per se produces not increased numbers of lymphocytes but histiocytes."

A conception similar to that of Gittins and Hawksley was put forward by Joan Ross,<sup>14</sup> who emphasized the difference between endothelium (the lining of the ordinary blood and lymph channels) and "sinus reticulum" or "littoral" cells, the cells lining the sinuses of the spleen, the bone marrow, the lymph nodes and so on. Of course, this may be merely another way of designating the conception of reticulo-endothelial endothelium, but perhaps it is important to use a term

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13 Gittins, R., and Hawksley, J. C. Reticulo-Endotheliomatosis, Ovarian Endothelioma and Monocytic (Histiocytic) Leukemia, *J. Path. & Bact.* **36** 115 (Jan.) 1933

14 Ross, J. M. The Pathology of the Reticular Tissue Illustrated by Two Cases of Reticulosis with Splenomegaly and a Case of Lymphadenoma, *J. Path. & Bact.* **37** 311 (Sept.) 1933

which automatically creates a distinction between the endothelium of the common blood vessels and the cells lining the sinuses of the spleen, liver, lymph nodes and bone marrow. The accompanying diagram (fig 1) is an attempt to represent the development of the leukocytes as conceived by Ross.

The truth is, of course, that the problem is still seen "through a glass darkly." With all of the improved technical methods of study, one cannot clearly trace the origin and interrelationships of the important group of cells which have been variously termed large mononuclear cells, macrophages, polyblasts, endothelial leukocytes, histiocytes, clasmatocytes, adventitial cells, reticulo-endothelial cells and monocytes. But in spite of the hiatuses in the knowledge of these cells, there is a mounting tendency to postulate the existence of a third hematopoietic

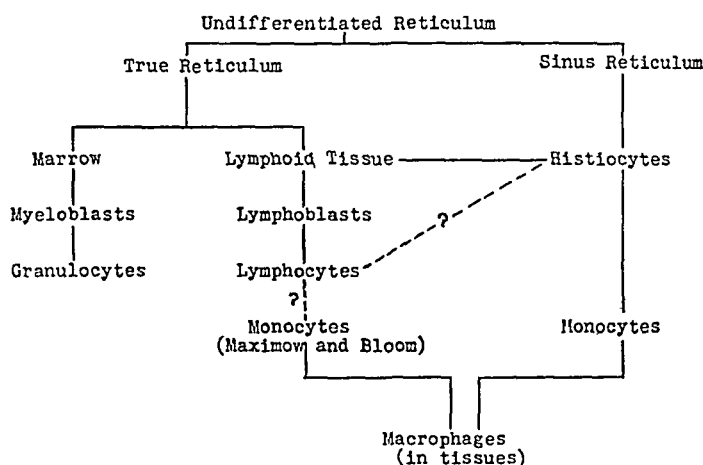


Fig 1—Diagram showing the development of the leukocytes as conceived by Ross.<sup>14</sup>

(monocytopenic) system which is closely related to what is known as the reticulo-endothelial system, the proliferation of which may give rise to characteristic changes in the blood and in certain other tissues which are recognized as monocytic leukemia, as leukemic reticulo-endotheliosis or as leukemic sinus reticulosis (Ross' term).

#### CLASSIFICATION AND TERMINOLOGY

Systematic classifications of the hyperplasias of the blood-forming organs have followed many vogues. Most of the investigators have erected their schemes on Aschoff's conception of the reticulo-endothelial system. Foord, Parsons and Butt<sup>10</sup> recently advanced a modified classification of this kind. Ross<sup>14</sup> expressed the opinion that such an approach does not allow sufficiently for the developmental possibilities of the cells of the stroma (reticular cells) of the hematopoietic organs. She proposed a classification based on Maximow's theory of the multi-

potential capacity of the reticulum for differentiation. Her tabulation slightly abbreviated, follows

# I Without Disturbance in Metabolism<sup>15</sup>

## A True Reticuloses

Hyperplasia affecting undifferentiated cells with unrestricted potency for differentiation, i.e., follicular reticulum of lymph glands, malpighian bodies of spleen and undifferentiated reticulum cells of connective tissue

- 1 Lymphoid
- 2 Fibrillary
- 3 Histiocyte
- 4 Myeloid
- 5 Giant cell
- 6 Fibrillary plus giant cell
- 7 Unrestricted differentiation of cells (lymphadenoma)

## B Sinus Reticuloses

Hyperplasia affecting cells already specialized, i.e., sinus reticulum (littoral cells)

- 1 Leukemic (monocytic leukemia)
- 2 Aleukemic

# II With Alteration in Metabolism

Hyperplasias of reticulum cells with differentiation to histiocytes which store various substances (usually lipoids)

- A Storage histiocytoses
- B Lipoid histiocytoses
- C Lipoidoses

(Gaucher's disease, Christian's syndrome, xanthomatosis, Niemann-Pick's disease, hypercholesterolemic splenomegaly)

It will be seen at once that this classification assumes in harmony with Maximow's theories, that the venous sinuses of the spleen and bone marrow and the lymph sinuses of the spleen and lymph glands are lined by differentiated reticular cells. These cells are similar to the Kupffer cells of the liver. Like the Kupffer cells, these reticular cells are phagocytic, and they are probably entirely different from the endothelial cells lining ordinary blood and lymph channels. To call both groups of cells "endothelial" is confusing. The cells of the sinus reticulum have been aptly termed littoral (seashore) cells (Siegmund,<sup>16</sup> 1925). The use of such a term may tend to discredit the popular conception that all blood and lymph channels are lined by the same kind of "endothelium."

As early as 1924, Letterer<sup>17</sup> suggested that a distinction should be drawn between reticulum and reticulo-endothelium (sinus reticulum)

<sup>15</sup> "In group I localized tumour formation might be expected in some cases" (Ross<sup>14</sup>)

<sup>16</sup> Siegmund, H. Verhandl. d. deutsch. path. Gesellsch. **20** 260, 1925, quoted by Ross<sup>14</sup>

<sup>17</sup> Letterer, E. Aleukämische Retikuloze, Frankfurt Ztschr. f. Path. **30** 377, 1924



in the classification of the systemic diseases of the reticulo-endothelial system. We have mentioned MacCallum's<sup>11</sup> objection to the term reticulo-endothelium on the ground of its evasiveness. The term groups together two tissues which, though related, are better kept in mind as distinct because they perform different functions and probably (as Ross suggested) respond independently to pathogenic factors. Sinus reticulum is chiefly involved in the reaction to pigments and dusts, in Addison's disease, in syphilis and in typhoid. The true reticulum of the follicles is involved in cases in which the lymph glands drain a pyogenic infection and in glandular fever (Pratt,<sup>18</sup> 1931). Ross assumed this reactive specificity to be true of the hyperplasias of the reticulum of the blood-forming organs, and her classification emphasizes this theory.

If Ross' conclusions are accepted, the sinus reticulum is to be regarded as the third hematopoietic system, and monocytic leukemia is extricated from the too large group of reticulo-endothelioses to become known as leukemic sinus reticulosis. This term is descriptive and distinctive, it represents the best approximation to the real nature of the condition which the present knowledge permits.

#### LEUKEMIA

*Nature of Leukemia*—In spite of certain obvious resemblances to an inflammatory condition (such as the presence of fever, leukocytosis and so on) there are good grounds for regarding leukemia as a malignant neoplastic process. In his recent series of Colver lectures delivered at the College of Medical Evangelists, Dr. William Boyd<sup>19</sup> proposed that the generic term leukemia should not be allowed to lead workers to the supposition that the members of the group of the leukemias are intimately related or that other conditions cannot be closely related simply because they do not exhibit similar hematologic phenomena. Probably lymphoid leukemia has a more fundamental resemblance to lymphosarcoma than it has to myeloid or monocytic leukemia or to erythremia. The evidence for this probability is strengthened by the work of Furth, Seibold and Rathbone,<sup>20</sup> who studied experimentally produced lymphomatoses (lymphatic neoplasms with or without leukemia) in mice. They concluded.

Leukemic lymphomatosis (lymphoid leukemia), aleukemic lymphomatosis, lymphosarcoma, and leukosarcoma are malignant processes, they are different manifestations of the same disease. Leukemic lymphocytes are not lymphoblasts but malignant (pathological) lymphocytes with limited power of maturation,

18 Pratt, C. L. G. Pathology of Glandular Fever, *Lancet* **2** 794 (Oct. 10) 1931.

19 Boyd, W. Lectures to be published.

20 Furth, J., Seibold, H. R., and Rathbone, R. R. Experimental Studies on Lymphomatosis of Mice, *Am. J. Cancer* **19** 521 (Nov.) 1933.

and when these cells multiply, their characteristics persist. These characters determine their ability to produce tumors, to invade the blood stream, to transmit the disease to related or unrelated mice, to localize in certain organs, etc. The essential change in leukemia consists not in the appearance of immature blood cells in the circulation (analogous to the "shift to the left" of Arneth), but in invasion of the blood stream by malignant lymphocytes.

Gittins and Hawksley<sup>13</sup> recently reported a case of "reticulo-endotheliomatosis, ovarian endothelioma, and monocytic (histiocytic) leukemia." They regarded their case as evidence in favor of the essentially neoplastic nature of monocytic leukemia, though they remarked that "considering the mesenchymal origin of endotheliomata and sarcomata on the one hand and blood cells on the other, lack of clinical association between the two is surprising."

If the theory is accepted that the essential process in any type of leukemia is a malignant neoplasia of the particular hematopoietic tissue with the invasion of the blood stream by characteristic malignant cells, one must admit that the most disturbing fact opposing the theory is the infrequency of specific focalization. Malignancy and neoplasia are closely associated in the minds of investigators with infiltration and with localized tumor formation. However, this association may not be as close as has been supposed. Even if the relation is essential, one may support the theory of malignant neoplasia by pointing to the well recognized occurrence of leukemia with chloroma and with lymphosarcoma, to the occurrence of myeloma in myeloid leukemia (true myeloid myeloma has been described, MacCallum<sup>11</sup>) and to the occurrence of the tumor in monocytic leukemia described by Gittins and Hawksley<sup>13</sup> which is similar to the lesion in the present study.

Perhaps it is time that the leukemic phase of the permanent hyperplasia of the blood-forming organs be regarded as of great diagnostic significance but of small pathologic importance. The malignant neoplasia seems the essential process (certainly no other word than "malignant" could imply the inexorable mortality of 100 per cent), the leukemia seems more or less incidental. In other words, leukemia is not a disease of the blood nor, indeed, a disease at all, it is probably the reflection in the blood stream of a hidden malignant change affecting the hematopoietic cells of a fixed line of development (myeloid, lymphoid or sinus reticulum). Sometimes evidence of this neoplasia may be seen in the form of tumor growth. In this communication an arresting example of such a tumor is described which occurred in a case of leukemic sinus reticulosis (monocytic leukemia).

#### CLINICAL FEATURES

We have stated that the most enlightening pathologic name for permanent hyperplasia of the monocyte-producing tissue is leukemic

sinus reticulosis Clinically, however, there is considerable justification for the older name—monocytic leukemia The morphologic recognition of immature (probably malignant) monocytes in the blood is still the single pathognomonic means of antemortem diagnosis There are no other clinical characteristics of the disease which may be relied on to differentiate monocytic leukemia from the other leukemias<sup>21</sup> Therefore, the term monocytic leukemia serves a useful clinical purpose in stressing the one practicable diagnostic procedure

The onset is usually gradual, with inexplicable fatigue, though it may be acute Some degree of fever is almost constant, in the acute cases, the temperature may be high At some stage in the process, gingivitis is nearly always present The gums swell, they often ulcerate and bleed Adenopathy is variable Theoretically, slight enlargement of the spleen and of the liver should be present and has been noted in most of the recorded cases, but, in our opinion, the ability to detect slight enlargements of the liver and of the spleen varies too much with the individual examiner to be of great value Petechiae and purpuric manifestations frequently occur The duration of the disease is from two to thirty weeks, with an average of ten weeks (Dameshek<sup>9</sup>)

Microscopic examination of the blood usually reveals secondary anemia and monocytic leukocytosis (though aleukemic cases have been reported, for example, that of Letterer<sup>17</sup>) The total white cell count has been found to range from 2,000 (Wyschegorodzowa<sup>22</sup>) to 416,000 (Swirtschewskaja<sup>23</sup>), but the count tends to be lower than that of the other two leukemias

The differential count of the white cells usually shows that from 50 to 75 per cent are of the monocyte type It is usually stated that the monocytes in monocytic leukemia are of two varieties (1) the monocyte of the normal blood and (2) a more immature cell, the histiocyte assumed to be the forerunner of the monocyte (Dameshek) It is just as probable that the second type of cell is not the ordinary histiocyte (reticulo-endothelial cell, active or resting wandering cell or

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21 Since this manuscript was prepared for publication an article has appeared by Claude E Forkner (Clinical and Pathologic Differentiation of the Acute Leukemias, *Arch Int Med* **53** 1 [Jan] 1934) This writer expressed the belief that it is often possible to distinguish clinically the three main types of acute leukemia He thinks that the diffuse swelling of the mucous membranes, particularly of the gingivae, usually accompanied by ulceration and necrosis, is characteristic of acute monocytic leukemia

22 Wyschegorodzowa, W D Sur Frage der monozytaren Leukämie, *Folia haemat* **38** 355 (July) 1929

23 Swirtschewskaja, B Leukemic Reticulo-Endotheliosis (Monocytic Leukemia) A Disease of the Reticulo-Endothelial System, *Virchows Arch f path Anat* **267** 456, 1928

clasmatocyte) but a cell produced by rapid, disorderly proliferation (a malignant process) of the sinus reticulum, the assumed site of origin of the monocyte

The all-important diagnostic point is the accurate recognition of the monocyte, and this usually is not difficult. Monocytic cells are larger than other normal blood cells (in dry smears the diameter may be from 30 to 40 microns). The protoplasm is far more abundant than that of lymphocytes, so that the nuclei are relatively smaller. The nuclei are oval or kidney-shaped, and there is a tendency to horseshoe configuration in the older forms. When the Wright or the Giemsa stain is used, the cytoplasm has a typical ground glass appearance and is blue-gray. Azuric granules, when present, are massed around the nucleus, leaving a nongranular periphery. The chromatin of the nucleus is spun into a fine meshwork (coarser in the older cells) which creates an appearance of homogeneity. The color of the nucleus is violet. Pseudopodia are often seen. In moist preparations the monocytes evince marked motility, and if they are stained supravitaly, active ingestion of dyes may be observed. The Wright or the Giemsa stain alone is sufficient to identify the cells in a clearcut case, but sometimes the oxidase reaction helps to differentiate monocytes from lymphocytes and from myelocytes. (Monocytes usually give a negative oxidase reaction. If they give a positive oxidase reaction, the granules are small and infrequent.)

Beside the other types of acute leukemia, agranulocytosis and acute infections with accompanying monocytosis may have to be differentiated. The appearance of large numbers of immature monocytes (histiocytes or malignant (?) monocytes) and the progressive course to a fatal termination readily exclude the diagnosis of benign monocytosis. Agranulocytosis (malignant neutropenia) as a rule results in complete disappearance of the granulocytes, this condition is never seen in monocytic leukemia.

#### HISTOLOGY

Collections of large mononuclear cells resembling the monocytes of the blood are found in the lymph nodes, the spleen, the periportal spaces of the liver, the kidneys, the bone marrow and the reticular perivascular stroma of practically all of the organs. In the spleen and in the lymph nodes this proliferation and infiltration are so marked as to efface the normal architecture. Slight myeloid hyperplasia, especially in the spleen, has been noted by a few observers. Ross<sup>14</sup> expressed the opinion that some of the reported cases are carefully enough described from a histologic point of view as to make it possible to state that the process affected particularly the littoral cells (cells of the sinus reticulum). The substantiation of her theory that specific factors produce specific involve-

ment of the "true" reticulum in some cases and of the sinus reticulum in others requires more accurate histologic investigation than has been made in most of the reported cases

#### MONOCYTIC LEUKEMIA WITH INTESTINAL OBSTRUCTION

We are not recording such a rare incidental lesion as intestinal obstruction in order to suggest a new sign characteristic of monocytic leukemia. Gastro-intestinal complications are not particularly characteristic of any of the leukemias. So far as is known, the only other example of intestinal obstruction recorded as bearing a causal relation to a disease possibly related to leukemia is that of amyloidosis of the intestines occurring in a case of multiple myeloma (Randall<sup>24</sup>). Of course, this lesion is probably by no means peculiar to multiple myeloma and is just as likely to occur in any wasting disease of long standing.

The only other report, to our knowledge of actual tumor formation in monocytic leukemia is a case described by Gittins and Hawksley<sup>13</sup>. A 1 year old child presented the typical blood picture of monocytic leukemia, diffuse reticulosis (so-called reticulo-endotheliosis) and bilateral ovarian tumors, each of which weighed 210 Gm. The tumors were composed chiefly of cells identical with those observed in the other tissues. These lesions seem exactly comparable to the intestinal tumor which we are describing. The two cases constitute evidence against the theory of infectious etiology. They argue in favor of the theory that monocytic leukemia is a neoplastic process. In terms of Ross' classification, they must represent either (1) a combination of true reticulosis (of the connective tissue reticulum of the rectal wall and of the ovaries) and of sinus reticulosis (monocytic leukemia) or (2) leukemic sinus reticulosis with metastatic blastomatous growths simulating those seen in chloroma.

#### REPORT OF CASE

*History*—Mrs. A., a white woman, aged 34, was admitted to the Glendale Sanitarium and Hospital on June 8, 1932. She was in active labor and eight hours after admission was delivered of a normal girl, weighing 5 pounds and 7 ounces (2,466.4 Gm). Numerous rectal examinations at this time revealed nothing abnormal. Unfortunately, no study of the blood was made. Repeated examinations of the urine revealed nothing significant. The mother and child were discharged on June 18, each in good condition, the mother passed through the puerperium uneventfully.

On June 2, 1933, almost one year from the date of the previous admission, the patient was admitted to the hospital complaining of abdominal pain with distention and obstipation. The past history revealed that she had had influenza, frequent

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24 Randall, O. S. Multiple Myeloma Complicated by Intestinal Obstruction Due to Amyloid Infiltration of the Small Intestine, *Am J Cancer* **19** 838 (Dec) 1933

colds and the "usual childhood diseases" The only child was well One abortion, in 1922, was self-induced Her husband and both of her parents were living and in good health

She thought that the present illness began in the latter part of January 1933, when she began to feel tired and listless and suffered attacks of "light-headedness" About this time she noticed constipation, which gradually grew worse She remembered no purpuric manifestations or bleeding from the gums

On May 28 she observed that the abdomen was distended It was almost impossible to obtain a bowel movement, even with the aid of cathartics On May 30 she took a bottle of magnesium citrate, on May 31, E-X-Lax, and on June 1, castor oil and a glycerin and turpentine enema, with no results The abdominal distention became marked, and when abdominal pain ensued she came to the hospital

*Physical Examination*—The physical examination on June 2 revealed a slightly pale, dyspneic, fairly well nourished woman The temperature was 99 F (37.2 C), the pulse rate, 72, the respiratory rate, 20, and the blood pressure, 136 systolic and 90 diastolic The abdomen was extremely distended, so that no accurate palpation could be performed The teeth and gums showed good hygienic care, there was no evidence of bleeding No ophthalmoscopic examination was made of the eyes The breath sounds were normal, dyspnea apparently being due to the abdominal distention The heart was not shown to be enlarged on percussion, there were no murmurs or arrhythmia

Rectal examination revealed a constricting mass located about 3 inches (7.62 cm) from the anus The mass was firm and surprisingly smooth, and it was impossible to pass the finger beyond it On proctoscopic examination the mucosa covering the mass was seen to be flecked with a few small bleeding points There was no ulceration

Bimanual examination was difficult because of the distention, but the uterus was found to be apparently normal in size and slightly retroverted Both of the adnexal areas seemed tender

A diagnosis was made of intestinal obstruction due to carcinoma of the rectum, though a rapid frozen section of a piece of tissue from the region of the mass was reported by the pathologist, Dr O B Pratt, as "showing the mucosa of the bowel to be without evidence of malignancy"

Chemical examination of the blood revealed nonprotein nitrogen, 34.2 mg per hundred cubic centimeters, and chlorides, 420 mg The results of the Wassermann test were negative

*Course*—On June 2, 1933, a left inguinal colostomy was performed by Dr G K Abbott, who reported the finding of a hard dense mass with a diameter of 1¼ inches (3.18 cm) in the anterior rectal wall which was adherent to the lower segment of the uterus and could not be moved The surface of the mass on the rectal side was smooth In the pelvis were palpated other nodules surrounding the rectum and behind the fundus of the uterus

The patient seemed to improve following the colostomy, and considerable fecal material was expelled through the colostomy tube

On June 6 the colostomy tube was removed, and a soft diet was prescribed On June 9 the patient began to vomit and appeared toxic The condition grew progressively worse in spite of repeated colonic irrigations On June 13 she complained of severe abdominal pain The abdomen was distended and silent She was taken to the operating room and catheter drainage of two loops of the small intestine was performed by reopening the recent abdominal incision On June 14 the patient died

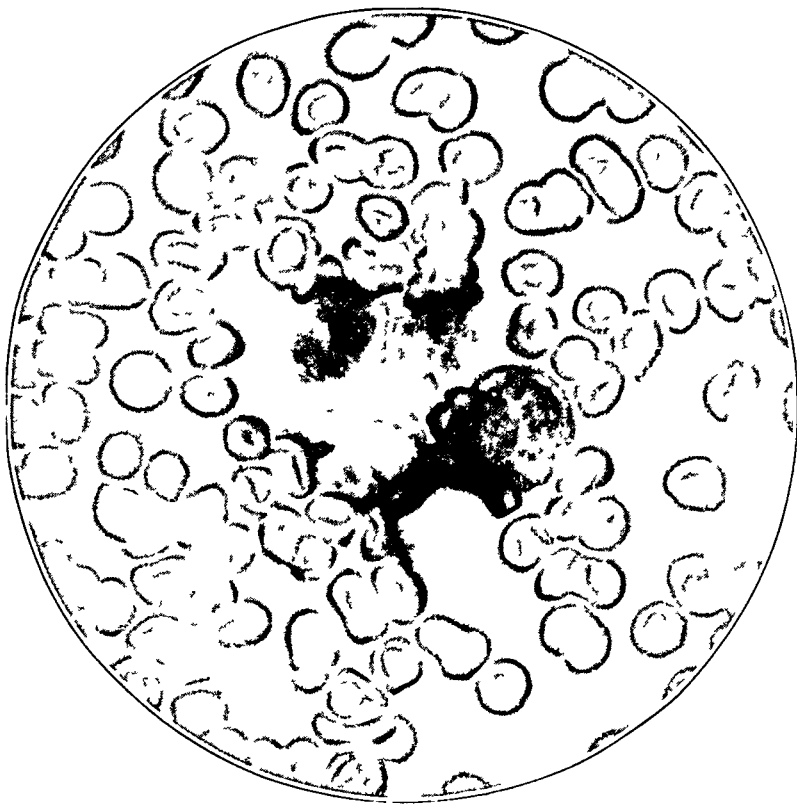


Fig 2—Photograph of a blood smear showing characteristic cells,  $\times 900$

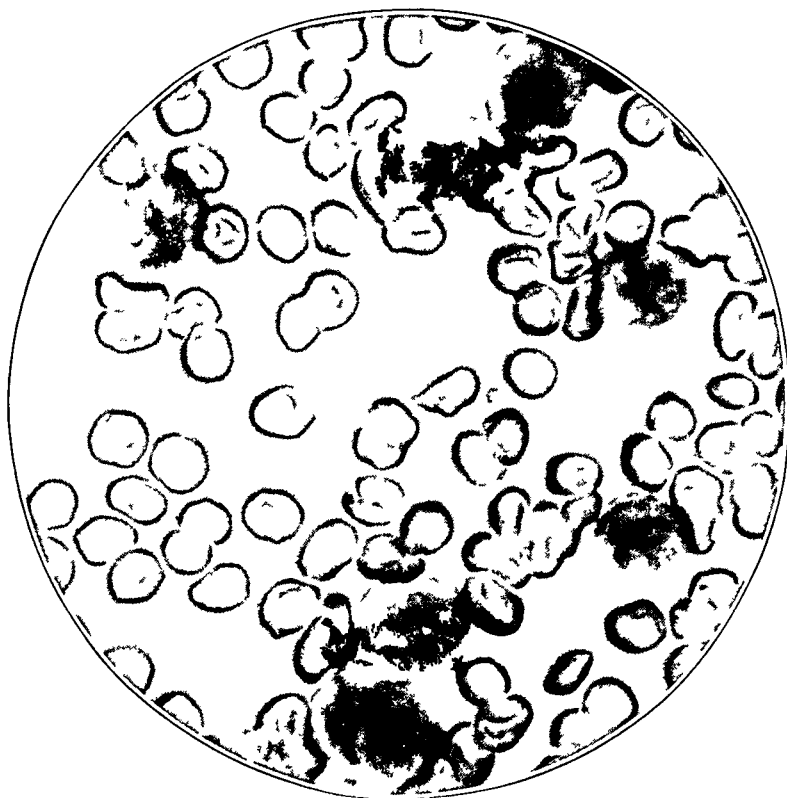


Fig 3—Photograph of a blood smear showing characteristic cells,  $\times 900$

*Autopsy*—Consent was obtained for a partial autopsy, which was performed by reopening the operative incision (Dr Janes). The uterus was slightly enlarged and symmetrical, and its posterior surface was densely adherent to a hard mass in the rectum. The wall of the rectum at this level was infiltrated and thickened. It measured about 2 cm in cross-section and almost completely obliterated the lumen of the bowel at this point. The fallopian tubes and the ovaries were normal in macroscopic appearance. The liver was smooth and presented no gross abnormalities. The spleen was moderately enlarged.

Consent was not obtained for the complete removal of any of the organs, neither was it possible to secure specimens of the bone marrow. However, blocks from the uterus, tubes, ovaries, rectum and spleen were saved for histologic examination. Sections of these tissues, with the blood smears were studied at the Los Angeles County Hospital by Dr T S Kimball (assistant pathologist) and by Dr R B Haining (resident in pathology). Their opinions were corroborated by Dr Newton Evans (chief pathologist), Dr O B Pratt and Dr Verne R Mason (Los Angeles), and Dr Alvin G Foord (Pasadena).

*Hemogram*—Several unstained smears made from the patient's blood on June 13, 1933, were submitted. The leukocytes in all of the smears were carefully studied (Dr Kimball), and in each case the monocytes were found to form from 75 to 90 per cent of the total leukocytes. The following differential count represents the average of several counts: polymorphonuclear neutrophils, 2 per cent, basophils, 1.5 per cent, eosinophils, 0, lymphocytes, 11 per cent, myelocytes, 0, myeloblasts, 0, mature monocytes, 36 per cent, immature monocytes, 49 per cent, and unclassified cells, 0.

*Microscopic Examination*—Rectal Wall. Examination with a hand lens showed the usual muscular wall with a well defined dark streak running lengthwise through the midportion of the muscle. The submucosa and the mucosa were replaced by a solid mass of tissue which took a darker stain than did the muscle fibers. This mass was homogeneous except for one round area 5 mm in diameter 1 cm from the muscular wall. Examination with a low power lens showed the dark streak in the muscular wall to be a zone of closely packed, fairly round cells which in some areas were perivascular but in others appeared to bear no relation to the vascular channels. From this band of cells there were many smaller extensions at right angles into the muscle bundles, giving the effect of a tree with many stubby branches. The smaller accumulations of cells were almost always associated with small blood vessels. A similar collection of cells was noted on the serous surface associated with the small blood vessels. The most striking feature, however, was the appearance of the mass of tissue which replaced the inner coats of the rectum. It was composed almost entirely of closely packed cells with little fibrous reticulum. Several fairly large blood vessels were present in this tumor, but the cellular collection was massive and no association with blood vessels could be demonstrated. The small round area seen with the hand lens appeared to be lymphoid tissue. Examination of the cellular detail by the oil-immersion and the high dry lens showed several interesting and, we believe, diagnostic facts. The cells were considerably larger than those seen in the usual case of myelosis or lymphadenosis with infiltration of tissue. The cytoplasm of each cell was more abundant than is seen in myelocytes or in myeloblasts and stained light pink with no demonstrable granules. The nuclei almost without exception showed notching or lobulation. There was a definite nuclear membrane with a few fine strands of chromatin throughout the nucleus, but with no large



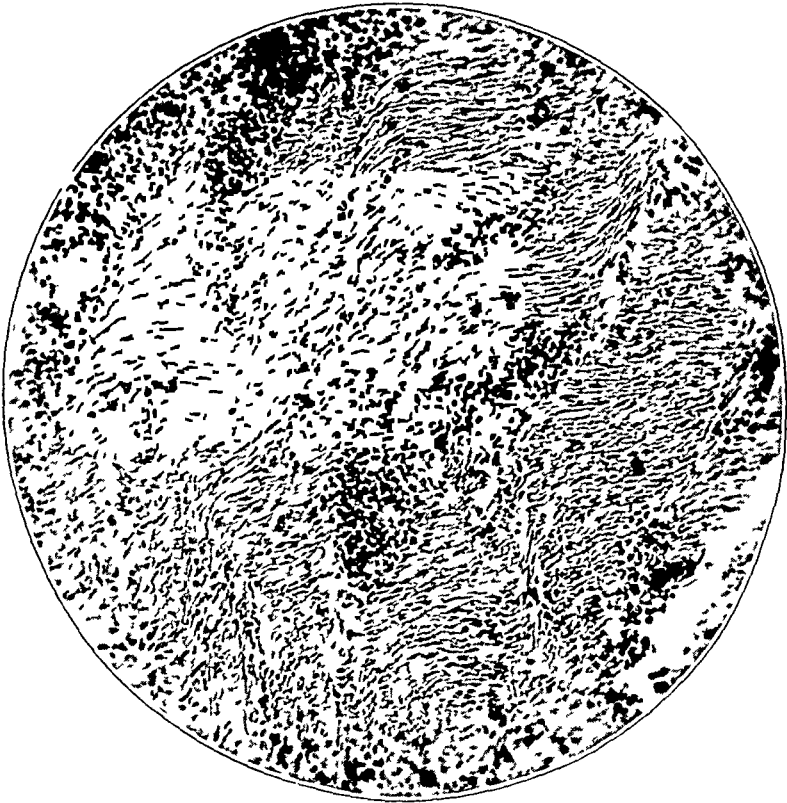


Fig 4—Photograph of a section from the rectal wall showing the marked cellular infiltration  $\times 120$

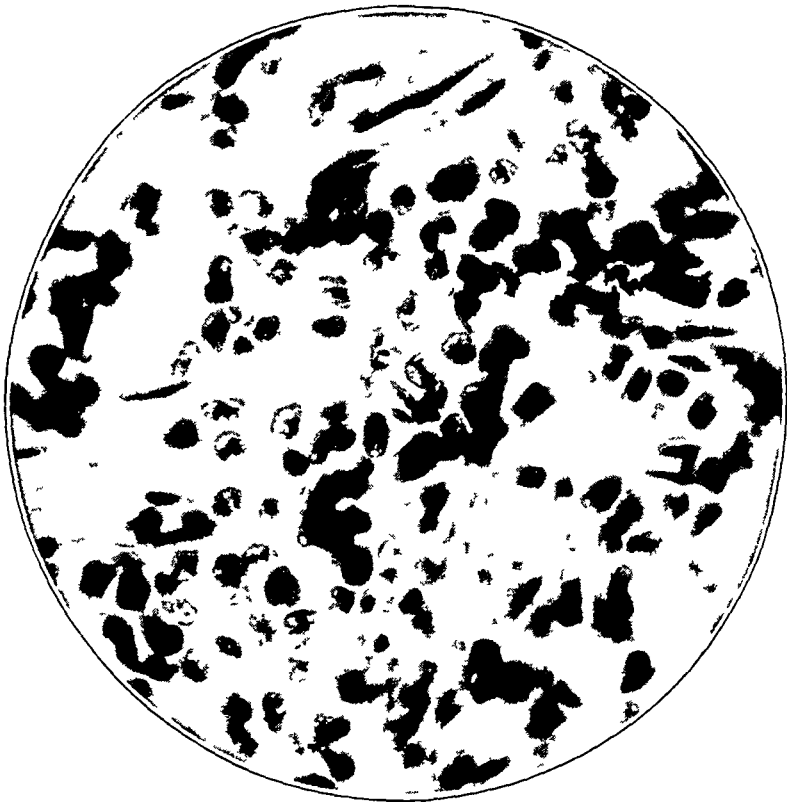


Fig 5—Photograph of tissue from the rectal wall showing greater cellular detail than figure 3,  $\times 500$

clumps. Nucleoli were conspicuously absent from the great majority of the cells. On the other hand, mitoses were numerous, showing great activity in the growth of the cells. The presence of so many mitotic figures suggests either development of the cells *in situ* or an infiltration of cells from the blood. If the latter view is correct, the cells were autonomous and had neoplastic faculties. A small percentage of smaller cells containing eosinophilic granules were present. No evidence could be observed that the endothelial cells within the blood vessels were actively growing and producing the typical cell. A fine hyaline reticulum appeared between nearly all of the cells, and a stain for reticulum showed a delicate reticular tissue pervading the entire mass with individual fibers around nearly every cell or, at the most, around each two or three cells. On comparing the structure of the small island of lymphoid tissue with that of the main tumor, a striking difference

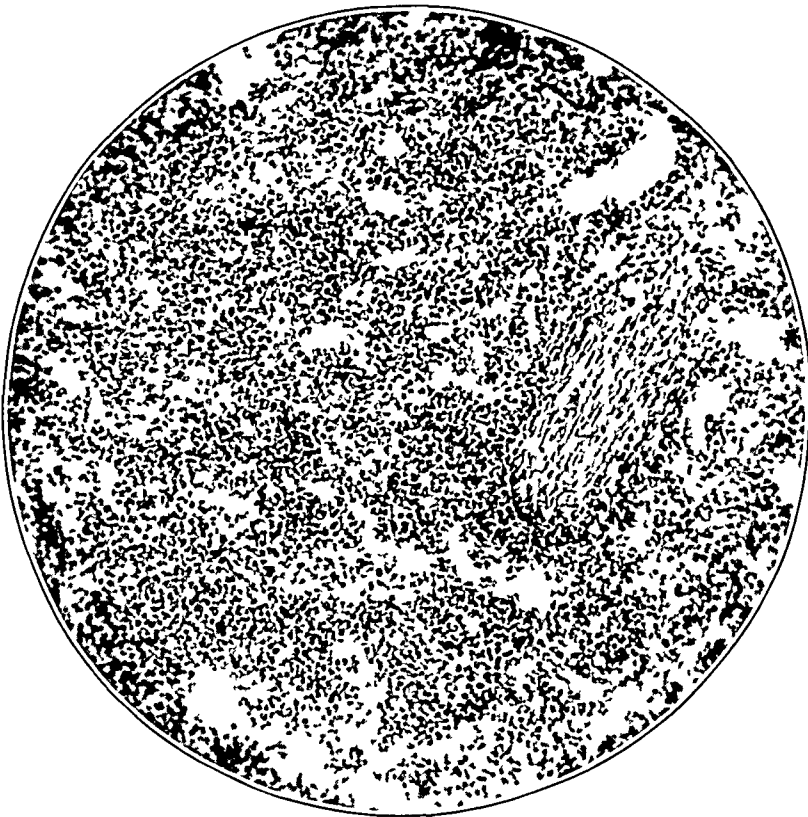


Fig 6—Photograph of tissue from the ovary showing cellular infiltration,  $\times 120$

was noted. In the lymphoid tissue only a small number of fibers was observed, all being uniform in size and in distribution.

**Spleen** The normal architecture was markedly altered, so that only an occasional small follicle was seen. The pulp was replaced by large numbers of cells corresponding to those in the rectal wall. The entire picture was that of a marked cellular hyperplasia in the pulp with replacement of many of the follicles. One curious feature was the apparently greater activity along the borders of the trabeculae, and in some instances there was an actual proliferation of cells in the trabeculae themselves.

**Ovary** Surrounding the entire organ just beneath the peritoneal coat was a thin zone of cells of the type already described. Active growth was evinced by the fact that large numbers of mitotic figures were present. In the deeper-lying tissues, especially in the follicular remains (*corpora albicantia*), other foci of

hyperplasia were noted. In fact, all through the densest portion of the cortex occasional mitotic figures and monocytic cells were seen.

**Uterus** Numerous collections of the typical cells were especially noticeable near the serous surface. These collections were almost invariably associated with small blood vessels. Unfortunately, the mucous surface was not included in the section submitted to us. Many of the small blood vessels in the muscular wall were filled with blood, and a high proportion of white cells were seen, which were mostly of the mononuclear type.

**Summary of Histologic Picture** The mucosal and the submucosal reticulosis assumed the proportions of a tumor, there was a diffuse reticulosis of the spleen, of the ovary and of the uterus.

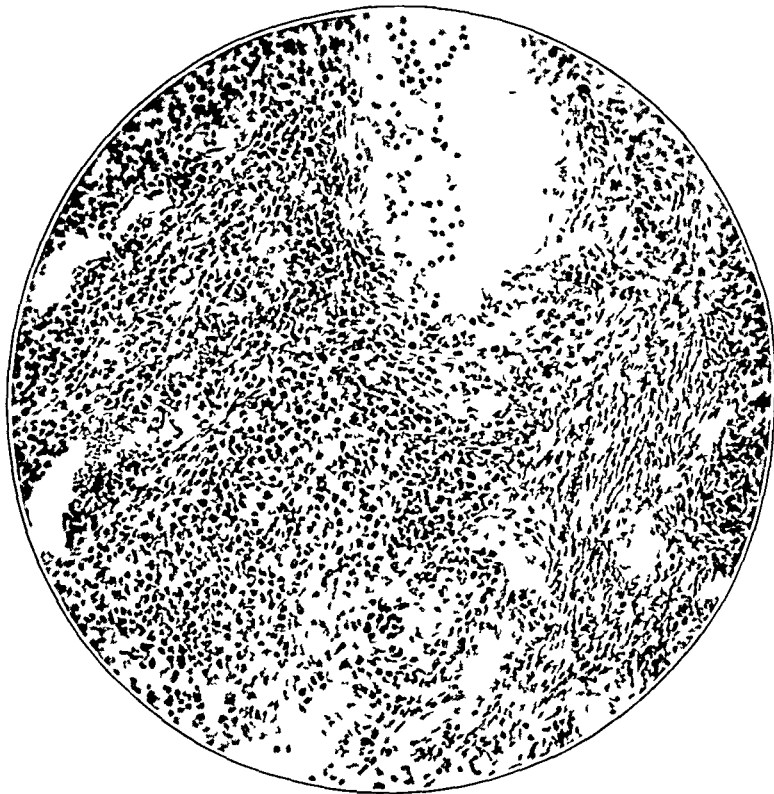


Fig 7—Photograph of tissue from the spleen,  $\times 120$

#### SUMMARY AND CONCLUSIONS

1 The venous sinuses of the spleen and of the bone marrow and the lymph sinuses of the spleen and of the lymph glands probably are lined by differentiated reticular cells. These cells are similar to the Kupffer cells of the liver. Like the Kupffer cells, they are entirely different from the endothelial cells lining the ordinary blood and lymph channels.

2 The term "reticulo-endotheliosis" applied to monocytic leukemia does not elucidate the fact that the endothelial cells lining the ordinary blood and lymph vessels have nothing to do with the process. Neither does it attempt to distinguish between true reticulum and sinus reticulum (reticulo-endothelium).

3 Monocytic leukemia is probably a sinus reticulosis, whereas myeloid and lymphoid leukemia are probably true reticuloses

4 There are good grounds for the conception that leukemia is a malignant neoplastic process. Malignant processes and neoplasia are closely associated in our minds with infiltration and with tumor formation. Specific focalization with tumor formation is apparently infrequent in leukemic sinus reticulosis (monocytic leukemia)

5 A case is recorded of acute monocytic leukemia in a young woman with localized mucosal and submucosal reticulosis in the rectal wall which assumed the proportions of a tumor. The tumor produced complete intestinal obstruction, clinically, the case exactly simulated carcinoma of the rectum with intestinal obstruction

NOTE—Since this article was prepared for publication another case of monocytic leukemia with formation of tumors has been observed at the Los Angeles County Hospital. The autopsy was performed by Dr. E. M. Butt, and tumors were noted in the pancreas, mesentery, heart, pleurae and diaphragm. The case will be reported later by Dr. Butt. Perhaps the occurrence of tumor formation in cases of monocytic leukemia is not as rare as has been supposed, and the lesion has possibly been interpreted as another type of neoplasm. The value of complete studies of the blood in all cases of tumors of obscure origin should be emphasized.

# XANTHOMATOSIS GENERALISATA OSSIIUM

## REPORT OF A CASE SIMULATING OSTEITIS FIBROSA CYSTICA

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AND

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BALTIMORE

Since the introduction of parathyroidectomy as a cure for osteitis fibrosa cystica by Mandl,<sup>1</sup> in 1926, interest in generalized bone diseases has increased greatly. The numerous chemical and clinical observations on Recklinghausen's disease since 1926 have established certain criteria for arriving at the diagnosis of hyperparathyroidism and for use as a basis for exploring and possibly removing one or more hyperfunctioning parathyroids. The disease is usually first recognized clinically either through the history of a fracture or pain in an extremity or by the presence of calcic deposits in unusual sites, such as the skin or pelvis of the kidney, and the diagnosis is further corroborated by the discovery of cysts or areas of degeneration as shown in roentgenograms of the bones. The final diagnosis however depends on the results of the determination of the calcium and phosphorus concentrations in the blood and excreta. The typical chemical findings in osteitis fibrosa are (1) hypercalcemia, (2) hypophosphatemia and (3) increased excretion of calcium in the urine, leading to (4) a negative calcium balance.

The typical cases of Recklinghausen's disease, presenting all the clinical and laboratory evidence indicative of hyperfunction of the parathyroids, offer little difficulty in diagnosis. However, cases of generalized disease of the bones, in which the cardinal clinical and laboratory signs are not clear, do present certain diagnostic problems. The difficulty may be due to several factors. Hypercalcemia, which is one of the most important diagnostic signs of hyperparathyroidism associated with osteitis fibrosa, has been encountered also in cases of multiple myeloma of the bones<sup>2</sup> and in cases showing osseous destruction as a result of infiltration or metastases by tumor cells.<sup>3</sup> Conversely, cases of Reck-

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From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics, Johns Hopkins University, and from the Kernan Hospital for Crippled Children and the Department of Orthopedics of the University of Maryland.

1 Mandl, F. Arch f klin Chir **143** 1, 1926.

2 Barr, D. P., and Bulger, H. A. Am J M Sc **179** 449, 1930.

3 Mason, R. L., and Warren, S. Am J Path **7** 415, 1931.

Recklinghausen's disease may pass through periods in which hypercalcemia is not pronounced or is absent, an example is the case described by Wilder<sup>4</sup> In this instance, high serum calcium levels were noted only after repeated chemical examinations of the blood The roentgenograms also are not always helpful in the differential diagnosis, since the lesions of the bones supposedly typical of osteitis fibrosa may be simulated by other dystrophies of the osseous system Similarly, the histologic structure of material obtained by biopsy from the bones and stained with the ordinary dyes may resemble that of osteitis fibrosa cystica, since fibrous replacement of osseous tissue is not pathognomonic of the histopathologic lesions of Recklinghausen's disease, as will be seen from the discussion of the case to be presented

The necessity of arriving at a correct diagnosis becomes significant when surgical intervention is considered If the osseous changes are due to hyperfunction of the parathyroids, parathyroidectomy is indicated, but if, on the other hand, the lesions in the bones are not associated with hyperparathyroidism, removal of parathyroid tissue is not to be considered

We have recently encountered a case of dystrophy of the osseous system in a boy of 14 in which the roentgenograms and histologic studies of material removed by biopsy from one of the bones strongly suggested that the patient was suffering from Recklinghausen's disease, but the normal concentration of calcium and phosphorus in the serum and the apparently normal urinary excretion of calcium argued against it A diagnosis of xanthomatosis generalisata ossium was finally made as the result of a second biopsy Xanthomatosis was not definitely considered at first because the typical signs of xanthomatosis associated with the Schuller-Christian syndrome, namely, involvement of the calvarium, exophthalmos, diabetes insipidus and xanthomatosis cutis were absent

#### REPORT OF CASE

S H, a white boy of 14, was transferred from the Kernan Hospital for Crippled Children to the Harriet Lane Home of the Johns Hopkins Hospital, Sept 26, 1933, for study and observation

His family and past histories were irrelevant His present malady began two years previously, at which time he fell off a hay-loft, from a height of about 6 feet (2 meters) He felt pain in the left hip but was able to walk away He was not aware of a fracture in the extremity, nor was he confined to bed immediately after the fall Shortly after the accident, a limp appeared in the left leg and the patient tended to support his weight on the opposite leg He consulted a physician, who referred him to the Emergency Hospital, Annapolis, for a roentgenographic examination Because of the peculiar structure of the bone and the presence of a fracture in the neck of the left femur noted in the roentgenograms the patient was sent to one of us (A F V) for orthopedic consultation, and admitted to the University Hospital for observation

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4 Wilder, R M Endocrinology **13** 231, 1929

The calcium concentration in the serum at that time was 10.9 mg per hundred cubic centimeters, and the cytologic appearance of the blood, except for a moderate secondary anemia, was essentially normal. The urine was also normal. Roentgen examination of the long bones revealed cystlike areas as well as areas of sclerosis. The calvarium was not involved.

The patient was subsequently admitted to the Kernan Hospital for Crippled Children, where he remained from April 4, 1933, until July 23. Roentgenograms taken during that time showed the same changes previously noted, namely, a healed fracture in the neck of the left femur and areas of rarefaction, cystic formation and fibrosis in the humeri, radii and ulnas. The calcium and inorganic phosphorus concentrations of the serum were again within normal limits. A biopsy was performed on the left radius and the material was sent to the University Hospital for examination. The tissue removed from what appeared to be a cystic area was glistening white, and fibrous in appearance and consistency. The histologic sections, stained with hematoxylin and eosin, revealed a predominance of fibrous tissue, intermingled with spicules of bone and a few giant cells. The spicules of bone were surrounded by osteoid borders. Some of the sections contained, in addition, large, pale-staining, reticulated cells, resembling the foam cells seen in lipoid histiocytosis. But because of the infrequency of these cells and the predominance of the fibrosis, the significance of the foam cells was not fully appreciated at the time. On the basis of the roentgenographic and histologic observations and in spite of the negative results of the determinations of the calcium and phosphorus contents of the blood, a diagnosis of osteitis fibrosa cystica was strongly considered, but parathyroidectomy was deferred pending the outcome of more complete chemical studies of the blood and excreta.

The patient was sent home for the summer months and appeared to be doing well. However, on Sept. 18, 1933, he was readmitted to the Kernan Hospital because of loss of weight and increasing difficulty in using the left leg. The diagnosis of osteitis fibrosa cystica was still considered, but before parathyroidectomy was attempted, he was removed to the Harriet Lane Home of the Johns Hopkins Hospital for a study of the calcium and phosphorus metabolism.

On admission to the Harriet Lane Home, the patient's state of health was found to be essentially the same as that at the Kernan Hospital. He appeared rather small and underdeveloped for his age. The skin was clear. The lymph glands were not enlarged, and there was no visible or palpable enlargement in the neck in the region of the parathyroids. The head was of normal size and contour. The heart and lungs presented no abnormal physical signs. The liver and the spleen were not enlarged. The reflexes were normal and equal on the two sides. There was a marked limp of the left leg, and the patient carried most of his weight on the right leg. Irregular cortical thickenings were palpated in the long bones, especially in the upper third of the left humerus, the left greater trochanter, the phalanges of both hands and feet and the left fourth rib. The bony enlargements appeared hard and not painful to pressure. Crepitation was not noted. The left hip showed a prominent trochanter and *coxa vara* with consequent limitation of abduction and internal rotation. There was a marked scoliosis with a tendency to curvature to the left, and both a real and an apparent shortening of the left leg of 3.5 cm. was observed.

The calcium and phosphorus concentrations on September 27 were 9.6 and 4.6 mg per hundred cubic centimeters, respectively, and on October 4, 9.8 and

3.8 mg The concentration of plasma phosphatase was 8.4 units (Bodansky<sup>5</sup>), and the concentration of the blood cholesterol 221 mg per hundred cubic centimeters. The cytologic appearance of the blood and the results of tests of renal function were normal, the Wassermann and tuberculin tests gave negative results.

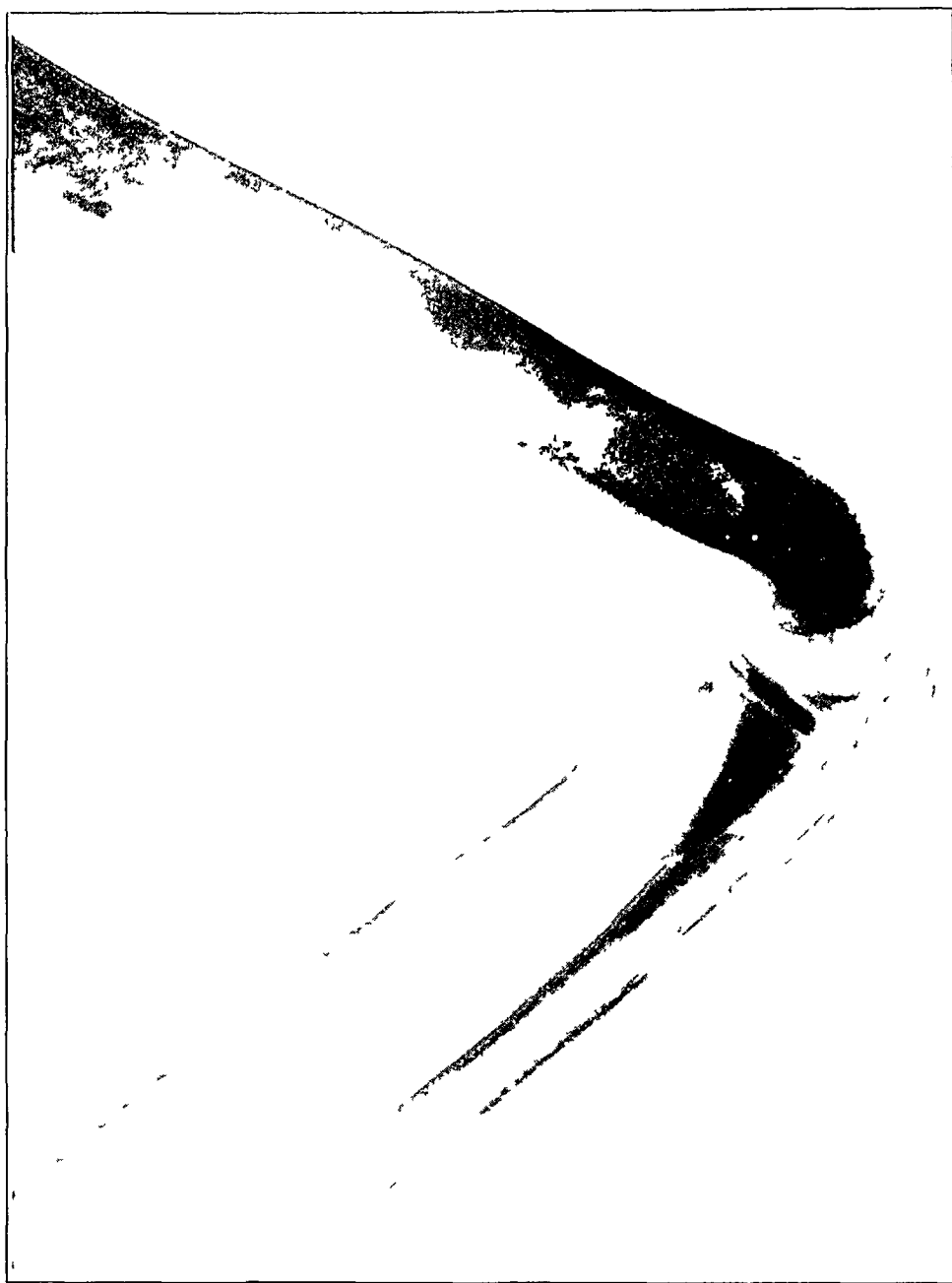


Fig. 1—Roentgenogram of the right humerus, radius and ulna. Note the cystlike areas at the elbow joint and the tendency to fibrosis, especially in the humerus.

The roentgenographic report was as follows: "There was a multilocular cystic involvement of the left femur with apparent pathologic fracture of the neck, the left ileum and the left and right humeri, radius and ulna showed similar processes.

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5. Milligrams per hour per hundred cubic centimeters of plasma.



The destructive process had apparently expanded and thinned the cortex of these bones, although in some areas there was evidence of fibrous replacement and sclerosis."

After a few days on the ordinary hospital diet the patient was placed on a diet containing only 200 mg of calcium daily. The urine was collected daily for a period of twelve days. The average daily excretion of calcium in the urine was 67.5 mg, the highest being 154.8 mg and the lowest 44.4 mg per day. The

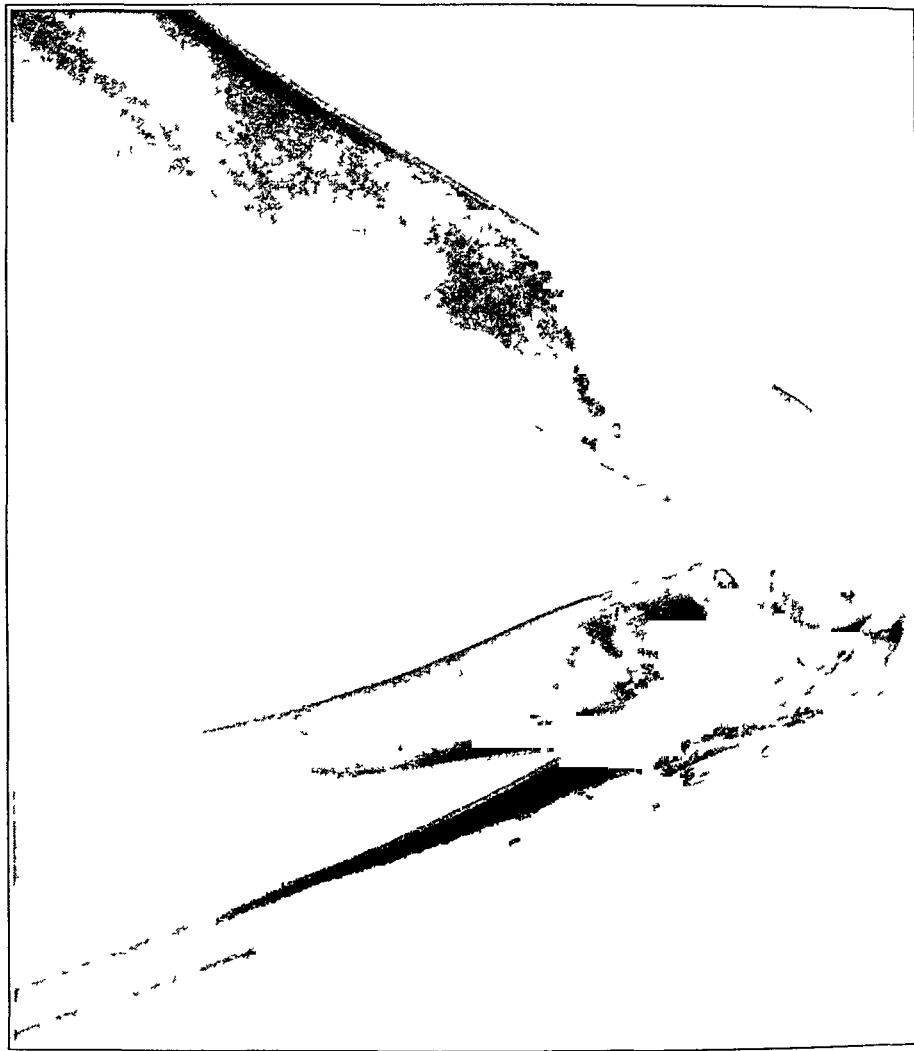


Fig 2—Roentgenogram of the left humerus, radius and ulna

excretion of phosphorus averaged 314.3 mg per day, the highest being 444 mg and the lowest 250 mg per day. Obviously, on this low calcium intake, the patient did not excrete excess amounts of calcium in the urine, as is usually the case in typical instances of Recklinghausen's disease.

During hospitalization and when at home, the patient showed no symptoms of polydipsia or polyuria. Xanthomatosis of the skin was also absent.

Reexamination at this time of the sections of the material obtained by biopsy led us to the conclusion that, in spite of the predominance of fibrosis and the presence of osteoid tissue, the numerous large, foamlike cells strongly suggested

that the lesions in the bones were in the nature of a lipid granulomatosis. As the biopsy material had been dehydrated by being passed through alcohol and hence was defatted the presence of lipid could not be determined by staining the remainder of the material with stains for fat. A second biopsy was, therefore, performed shortly after the patient returned to the Kernan Hospital. In contrast to the material obtained for the first biopsy, the tissue removed at the second

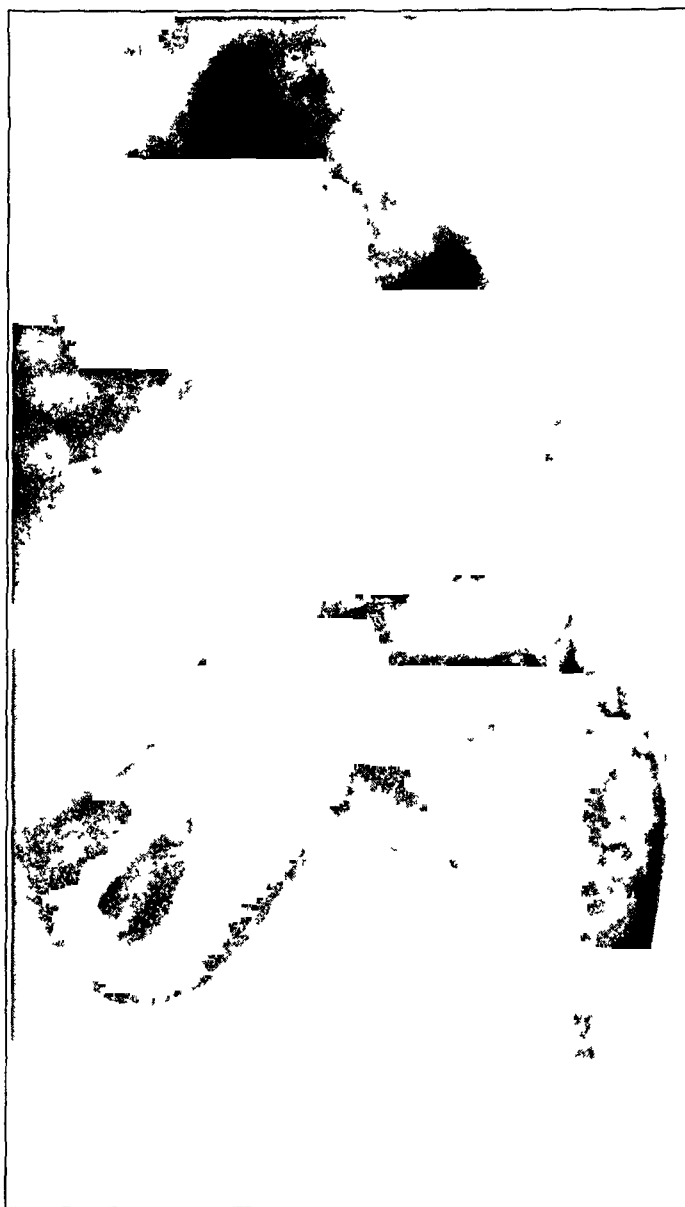


Fig 3—Roentgenogram of the left hip. Note the areas of rarefaction and the healed fracture in the neck of the femur.

operation was yellowish, granular and softer. Sections from this material were stained with sudan III as well as with eosin and hematoxylin. A description, by Dr. Paul G. Shipley, of the histologic appearance of this material follows.

In all sections, the spicules of bone appeared dense, obviously they must have been very hard. The endosteum was incomplete, and around most spicules of bone it was represented by a few scattered cells. The edges of the bony trabeculae

showed obvious signs of erosion, and in places one could see that the lacunae had been opened and the bone corpuscles left lying free. The lacunae were small, widely separated and few. Only occasional osteoclasts were present.

In the material examined at the first biopsy, some of the spicules of bone showed fairly wide osteoid borders as well as signs of former erosion. However, in the material studied at the second biopsy, osteoid tissue was absent. The meaning of this difference in the production of osteoid tissue is not clear. It is possible, however, either that different conditions prevailed in the different regions examined or that the osteoid tissue disappeared in the interval between biopsies, as a result of ultraviolet therapy.

The bony trabeculae in all the sections were widely separated by connective tissue, which in some areas was extremely dense. The fibers of the tissue were arranged in definite patterns between the spicules, often in broad, sweeping curves. The majority of these fibers seemed to be of the white variety. In certain areas, the fibers appeared to have undergone degeneration and to have become hyalinized. The cells of this tissue were numerous and consisted chiefly of connective tissue corpuscles. No traces of marrow were seen in the areas of fibrosis. Groups of cells, apparently osteoblasts, were present here and there.

The areas of fibrosis were fairly well vascularized by very small blood vessels, mostly capillaries. In some areas, the walls of the arterioles were unusually thickened, and in other places, the smaller arteries seemed to have participated also in this change. The nerves, when visible, had a normal appearance. Small hemorrhagic areas were seen in widely scattered areas of the connective tissue.

Parts of the intertrabecular tissue contained nests of huge cells with round or oval nuclei, usually eccentrically placed, and with a clear cytoplasm, which when stained with eosin and hematoxylin appeared to be a foamlike mass of tiny vacuoles (fig 4). In sections stained with sudan III, these vacuoles were seen to be droplets of lipid material. The nests of lipid cells were scattered throughout the dense connective tissue in groups of varying sizes, sometimes even singly (fig 5). These masses of foam cells undoubtedly represent xanthoma.

The grouping of these cells seemed to bear a definite relation to small blood vessels, which were wholly or partly surrounded by them. When a single xanthomatous cell existed alone, it was usually in apposition to a capillary.

On the basis of the histologic observations, and especially in the presence of an apparently normal amount of calcium and inorganic phosphorus in the serum and of a normal excretion of calcium in the urine, the diagnosis of xanthomatosis generalisata ossium seemed justifiable.

#### COMMENT

The case reported here illustrates the importance of considering lipid granulomatosis as a possible cause of cystic degeneration and fibrosis of the long bones. Attention has recently been directed to this fact by Snapper and Parisel.<sup>6</sup> Their patient, a girl of 10 years, was operated on twice but an adenoma of the parathyroid was not found. They were led to consider the possibility of xanthomatosis by obtaining, on one occasion, a cholesterol concentration in the blood of 322 mg per hundred cubic centimeters and also by Kienbock and Meworach's<sup>7</sup> discussion of the difficulties in differentiating xanthomatous lesions of the

6 Snapper, I, and Parisel, C. *Quart J Med* 2: 407, 1933.

7 Kienbock, R, and Meworach, L. *Rontgenpraxis* 4: 76, 1932.

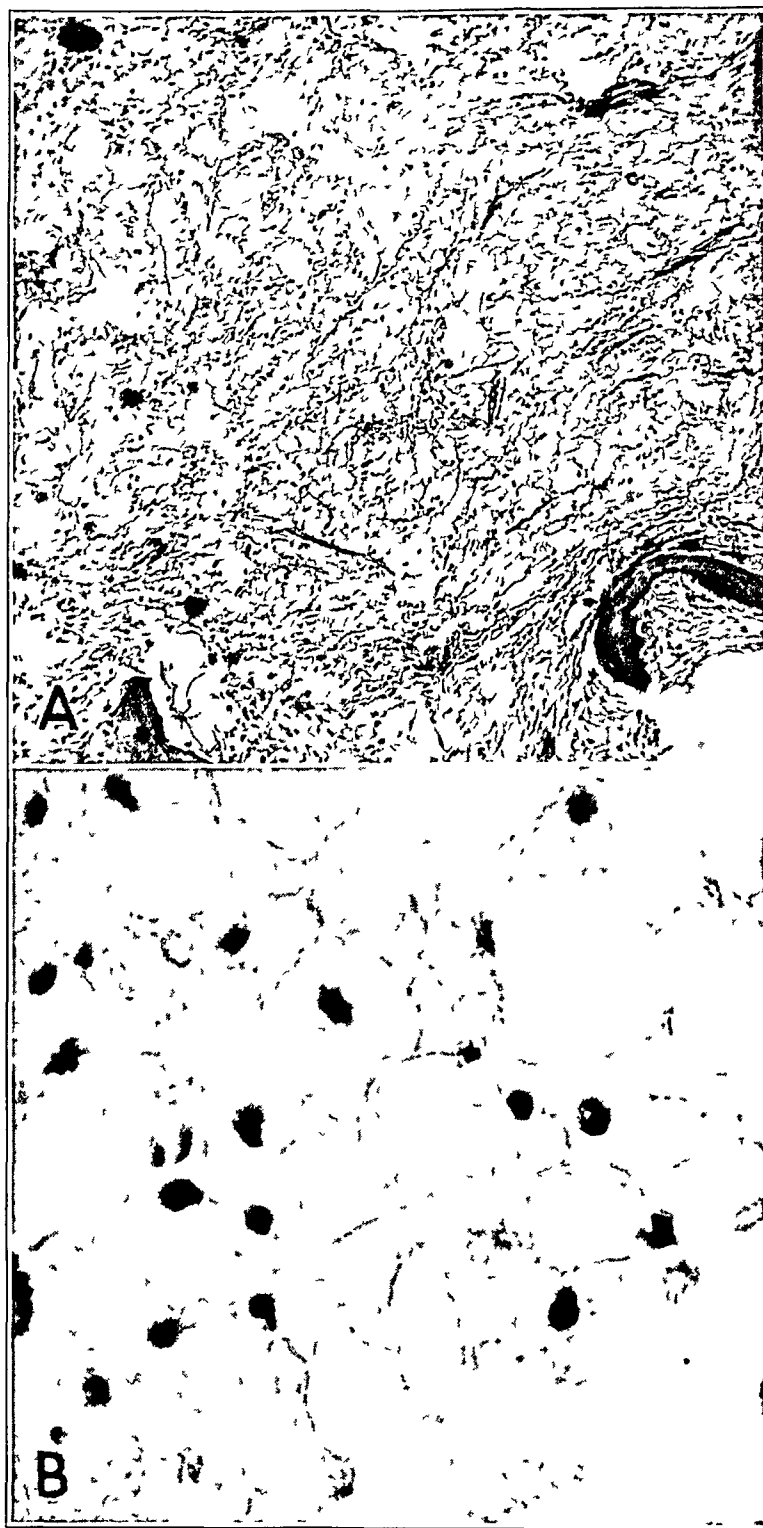


Fig 4—Sections of an area containing pale, large, reticulated foam cells *A*, under low magnification, and *B*, under high magnification. Hematoxylin and eosin stain.

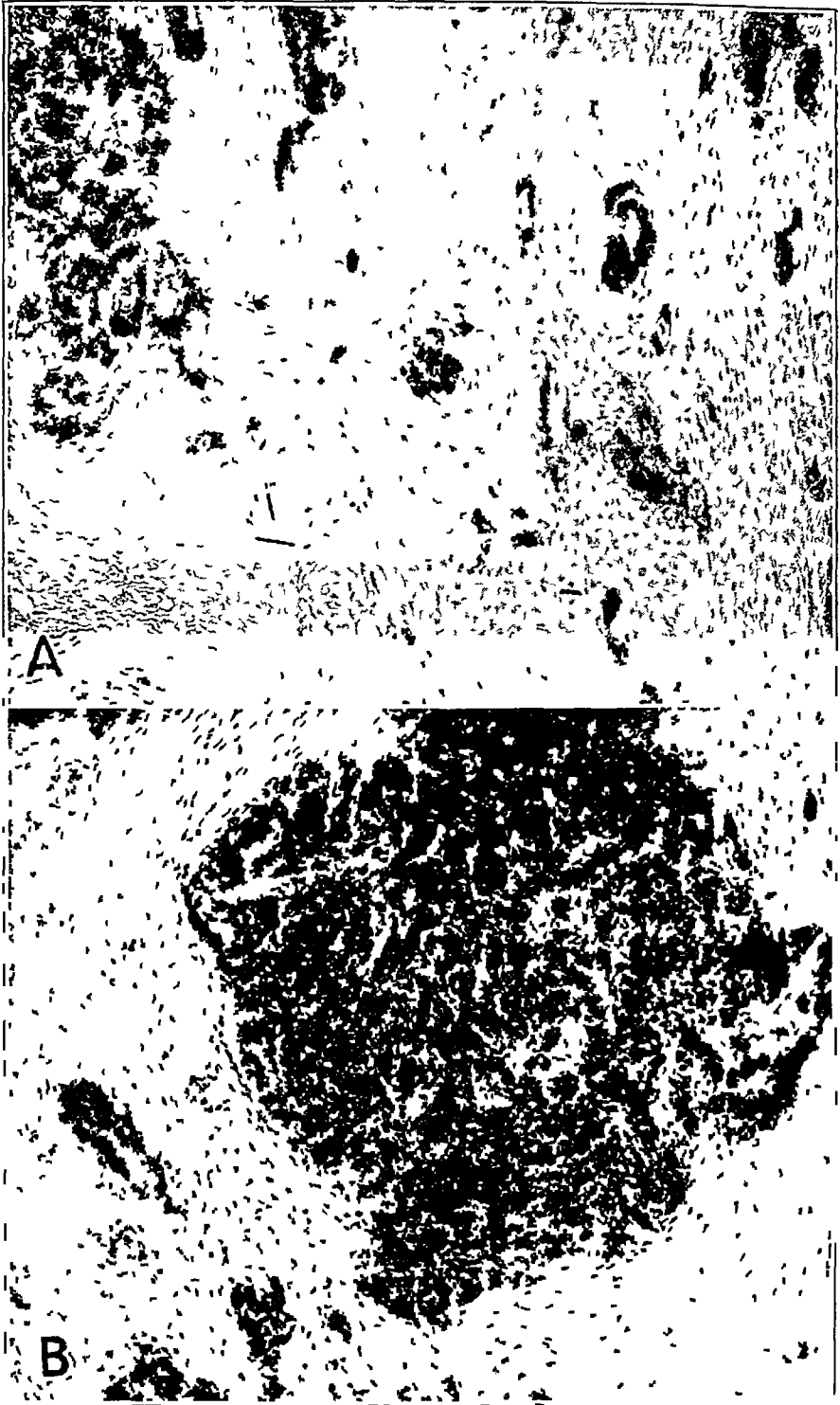


Fig 5—Islets of lipid in an area of fibrosis *A*, under low magnification, and *B*, under higher magnification (sudan III stain)

skeleton from true osteitis fibrosa cystica generalisata. The diagnosis was finally made, as in our patient, by a study of biopsy material removed for the second time from an affected bone. The histologic examination of this material showed "signs of osteitis fibrosa, but at the same time in the fibrous tissue great accumulations of foam cells loaded with double-refracting lipoids and fats."

Xanthomas are deposits of lipoids in large swollen foam cells; they appear yellowish in gross section. Chester<sup>8</sup> termed such deposits of fats "lipoid granulomatosis," as against the common designation of "tumors," since xanthomas consist primarily of granulation tissue and not of tumor cells. The lipoid is composed, according to Epstein and Lorenz<sup>9</sup> and Kleinmann,<sup>10</sup> of large amounts of cholesterol and its esters, as contrasted with lecithin in Gaucher's disease and keratin in Niemann-Pick's disease.

With the exception of xanthomatosis of the tendon sheaths, the most widely known clinical syndrome of xanthomatosis is Schuller-Christian's disease. Most of the cases belonging to this group possess the following clinical features: (1) multiple erosions of the bones of the skull, (2) exophthalmos, usually bilateral, (3) xanthomatosis cutis, (4) diabetes insipidus, and (5) retardation of growth, the majority of the patients being children. Xanthomatous infiltrations are also found, not infrequently, in the liver, spleen, lungs, kidneys and other organs of patients dying of the disease. The combination of xanthomatosis of the skull, skin and internal organs is not constant, and variations thus occur from the typical Schuller-Christian syndrome. (1) Xanthomatosis may be limited to the skin or internal organs without involving the bones, (2) it may be present in the long bones, as well as in the skull, skin and internal organs, or (3) it may be confined to the bones, or even to the long bones. In the past year, we have had occasion to observe three cases of xanthomatosis, including the present case, in which the symptoms were quite dissimilar. One presented xanthomatosis cutis and diabetes insipidus, without bone lesions, another showed the typical findings of Schuller-Christian's disease, including erosions of the long bones, whereas the case discussed here showed lesions of the long bones only, without involvement of the skin, internal organs or skull.<sup>10a</sup>

8 Chester, W. *Virchows Arch f path Anat* **279** 561, 1930.

9 Epstein, E., and Lorenz, K. *Ztschr f physiol Chem* **190** 44, 1930.

10 Kleinmann, H. *Virchows Arch f path Anat* **282** 613, 1931.

10a One of us (D. H. S.) recently saw another case of xanthomatosis ossium in which the lesions were limited to the calvarium, the left femur and the right clavicle. There were no other signs of Schuller-Christian's disease, and the concentrations of calcium and inorganic phosphorus of the serum were normal. Histologic sections, made from material removed for biopsy from a cystlike area in the clavicle, showed typical areas of xanthomatosis. The lesions healed under roentgen therapy.

Instances of other clinical and pathologic combinations have been collected by Henschen <sup>11</sup>

Instances of xanthomatosis cutis and diabetes insipidus, without osseous erosions, are rather rare. They have been noted by Ausset,<sup>12</sup> Crocker,<sup>13</sup> Turner, Davidson and White,<sup>14</sup> Spillman and Wartin<sup>15</sup> and Pusey and Johnstone.<sup>16</sup> However, xanthomatous involvement of the long bones, in addition to that of the skull, skin and internal organs, is more common. Thus, in Hertzenberg's<sup>17</sup> case, xanthomatous tissue was present also in the femurs and vertebrae. In Hofer's<sup>18</sup> case, in the bone marrow, and in Moreau's<sup>19</sup> case, in the left ilium. Similar lesions of the long bones in addition to those of the cranium were also noted by Pende,<sup>20</sup> Barco,<sup>21</sup> Cignolini,<sup>22</sup> Alberti,<sup>23</sup> Schultz, Wermbter and Puhl,<sup>24</sup> Thompson, Keegan and Dunn,<sup>25</sup> Veit,<sup>26</sup> Rowland,<sup>27</sup> Sosman,<sup>28</sup> Ighenti,<sup>29</sup> Chester and Kugel,<sup>30</sup> Merritt and Paige<sup>31</sup> and Henschen.<sup>11</sup> In several of these cases, the roentgenograms of the long bones showed a great similarity to those of osteitis fibrosa, but the diagnosis of xanthomatosis was

11 Henschen, F. *Acta pædiat* (supp. 6) **12** 1, 1931

12 Ausset, quoted by Henschen <sup>11</sup>

13 Crocker, H. R. *Diseases of the Skin*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1903

14 Turner, A. L., Davidson, J., and White, A. C. *Edinburgh M. J.* **32** 153, 1925

15 Spillman, L., and Wartin, J. *Paris med* **35** 193, 1920

16 Pusey, W. A., and Johnstone, O. P. *J. Cutan. Dis.* **26** 552, 1908

17 Hertzenberg, H. *Virchows Arch. f. path. Anat.* **269** 614, 1928

18 Hofer, K. *Klin. Wchnschr.* **9** 1302, 1930

19 Moreau, J. *Arch. franco-belges de chir.* **32** 697, 1931. Gohen, A., Moreau, J., and Murdoch, J. *Rev. d'orthop.* **17** 714, 1930

20 Pende, N. *Riforma med.* **45** 20, 1929

21 Barco, P., cited by Snapper and Parisel <sup>6</sup>

22 Cignolini, P. *Radiol. med.* **16** 16, 1929

23 Alberti, O. *Radiol. med.* **11** 157, 1924

24 Schultz, A., Wermbter, F., and Puhl, H. *Virchows Arch. f. path. Anat.* **252** 519, 1924

25 Thompson, C. Q., Keegan, J. J., and Dunn, A. D. Defect of Membranous Bones, Exophthalmos and Diabetes Insipidus, *Arch. Int. Med.* **36** 650 (Nov) 1925

26 Veit, B. *Frankfurt Ztschr. f. Path.* **28** 1, 1922

27 Rowland, R. S. Xanthomatosis and the Reticulo-Endothelial System, *Arch. Int. Med.* **42** 611 (Nov) 1928

28 Sosman, M. C. *Am. J. Roentgenol.* **23** 581, 1930, Xanthomatosis, *J. A. M. A.* **98** 110 (Jan. 9) 1932

29 Ighenti, W. K. *Virchows Arch. f. path. Anat.* **282** 585, 1931

30 Chester, W., and Kugel, V. H. Lipoidgranulomatosis (Type, Hand-Schuller-Christian), *Arch. Path.* **14** 595 (Nov) 1932

31 Merritt, K. K., and Paige, B. H. Xanthomatosis (Schuller-Christian Syndrome), *Am. J. Dis. Child.* **46** 1368 (Dec) 1933

quite evident from the presence of other symptoms indicative of Schuller-Christian's syndrome

The third variation of xanthomatosis, namely involvement of the long bones without involvement of the skull or internal organs appears to be rare, but when present offers the greatest difficulty in differentiation from osteitis fibrosa cystica. A case of this type was reported by Kienbock and Meworach<sup>7</sup> in 1932, and another by Snapper and Parisel<sup>6</sup> in 1933. The case here reported is apparently the third instance in which the diagnosis of osteitis fibrosa cystica was first considered but the disease was subsequently demonstrated, histologically, to be xanthomatosis, or lipid granulomatosis of the bones.

Kienbock and Meworach's patient showed spontaneous fracture and cystic degenerations in the upper third of the left femur, as well as some cystic areas in the dorsal vertebrae. On the basis of the appearance of the bones in the roentgenograms, Kienbock originally diagnosed the lesions as those of osteitis fibrosa cystica, although the expansion of the femur was not as marked as in advanced cases of Recklinghausen's disease. Five months afterward, a swelling was noted in the tenth rib, part of which was resected and examined histologically. The diagnosis, however, still remained obscure until the tissue was examined by Maiesch, who finally established the diagnosis of lipid granulomatosis.

Snapper and Parisel's patient, a mentally retarded girl, fell and fractured the femur at the age of 7 years. During the following two years she had five fractures of both femurs, one while turning over in bed. She was treated with preparations of calcium and ultraviolet irradiations, which apparently greatly benefited her. She had no more fractures and was able to walk, although deformities of both femurs and shortening of one leg were evident. The right humerus appeared swollen on palpation but was not painful. Roentgenograms of the long bones revealed osteoporotic lesions resembling multiple cysts, most pronounced in the right humerus. In this bone the degenerative process was extensive and caused the almost complete disappearance of the cortex at the affected sites. The calcium concentration of the serum was 12.6 mg. A diagnosis of osteitis fibrosa cystica was made and the patient was operated on twice, but no adenoma of the parathyroid was observed, in spite of the fact that the second exploration was extensive and was performed by a surgeon experienced in operations on the parathyroid. The diagnosis of xanthomatosis was suggested, as previously mentioned, by the observation of a blood cholesterol concentration of 322 mg. per hundred cubic centimeters, and by the resemblance of the roentgenograms of the bones to those in Kienbock and Meworach's case of xanthomatosis. The diagnosis was finally established by histologic examination of tissue removed, for the second time, from an area of



degeneration of the bone and the observation in this tissue of foam cells and lipid-staining material

Perhaps the case of Kienbock and Schenck<sup>32</sup> may be regarded as one of xanthomatosis ossium, although histologic proof is wanting. Their report concerned the case of a woman of 28 who had a fracture of the right humerus in 1927. Roentgenographic examination at that time revealed the fracture and, in addition, several central cysts. In 1928, cysts were also found in the left humerus. A diagnosis of osteitis fibrosa cystica was made, and in 1930 the patient was operated on, but an adenoma of the parathyroids was not found. In 1932, she had another fracture of the right humerus and at this time the diagnosis of xanthomatosis was considered, but as a biopsy was not permitted it was not confirmed histologically.

Chester<sup>8</sup> accidentally discovered a lipid granuloma of the femur at autopsy on a man of 44. This led him to investigate for lipid granulomatosis the bones of patients with xanthelasma of the eyelids. His search yielded but one positive result. He found a lipid granuloma in the femur and another in the tibia of a man of 69. In neither of these cases were there signs of fracture or other clinical manifestations suggestive of involvement of the bones.

Localized xanthomatosis of a single bone has been described from time to time. Schroeder,<sup>33</sup> who reported the last case, mentioned four analogous cases described by Vermooten, Merrill, Kogius, and Zeyland and Dega. Schroeder's case also offered some difficulty in diagnosis. His patient had noted a swelling in the distal part of the fibula about seven years previously. A diagnosis of melanosarcoma was made after biopsy. Amputation was advised, but this was refused by the patient. Seven years later, a diagnosis of osteitis fibrosa was made and partly confirmed by histologic examination. The tumor was finally extirpated and was described by the pathologist as osteitis fibrosa with accumulations of cholesterol and foam cells.

Little is known of the etiology and pathogenesis of lipid granulomatosis. In some cases, lipemia with hypercholesteremia has been noted, and hence the disease is considered to be due to a disturbance in lipid metabolism. The lipemia, however, is not a constant characteristic, since the concentration of cholesterol in the blood seems to depend on the degree of activity of the granulomatous process. In the active stage, the cholesterol concentration in the blood may be high; during periods of quiescence, it may be within normal limits. In Snapper and Paisel's case, hypercholesteremia was noted only once, on other occasions, the cholesterol content of the blood was within the normal range. Tests

32 Kienbock, R., and Schenck, F. *Beitr. z. klin. Chir.* **156** 237, 1932.

33 Schroeder, F. *Arch. f. klin. Chir.* **168** 118, 1931.

for cholesterol tolerance performed by them also gave practically normal results. The cholesterol esters in the blood were, however, increased so that the greater portion of the lipoids of the blood consisted of cholesterol esters. Epstein and Lorenz<sup>9</sup> noted a similar disproportion between free cholesterol and cholesterol esters in the blood in cases of Schüller-Christian's disease, the concentration of the esters being nearly five times that of the free cholesterol. We have not determined the cholesterol esters in the blood of our patient, but the total cholesterol was only moderately elevated, 221 mg per hundred cubic centimeters.

The mechanism of the infiltration of lipoids in the bones is also obscure. Chester<sup>34</sup> has expressed the belief that the basic lesion in lipid granulomatosis is "a chronic, noninfectious, abacterial, inflammatory granuloma due to the deposition of various lipid substances in the involved tissues," and that the inflammatory exudate is "a response of the tissues to the lipid substances." He did not, however, venture an opinion as to the nature of the fibrosis ossium. The tendency of the lipid to segregate about blood vessels, observed by Snapper and Parisel and by us, suggests the possibility that the fibrosis is present before the lipid is conveyed for deposition in the proliferating connective tissue, but direct evidence for this suggestion is not available. We have attempted to produce infiltration of lipoids in the bones of rats by first inducing fibrosis by injections of parathyroid extract and then by feeding large amounts of cholesterol, but our efforts have been unsuccessful.

#### DIFFERENTIAL DIAGNOSIS

The difficulty in differentiating xanthomatosis ossium from osteitis fibrosa by roentgen, and even by histologic, examination demonstrates the necessity of complete studies of the metabolism of calcium and phosphorus and of staining the biopsy material for lipoids before parathyroidectomy is attempted. At this point it may be well to review the possible diagnostic points by which xanthomatosis may be differentiated from Recklinghausen's disease, although they are by no means infallible. They may be summarized as follows:

1. Pain. Absence of pain in the bones is infrequent in Recklinghausen's disease and common in xanthomatosis.

2. Swelling of the bones. In most cases of osteitis fibrosa cystica there are thinning of the cortex, expansion and swelling of the affected area and general osteoporosis. In xanthomatosis ossium, the swelling and expansion of the bone are usually slight or moderate, and the osteoporosis is localized.

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<sup>34</sup> Chester<sup>8</sup> Chester and Kugel<sup>30</sup>

3 Metastatic calcification Calcic deposits in the soft tissues or the formation of renal calculi is more common in hyperparathyroidism than in xanthomatosis ossium

4 Hypercalcemia and hypophosphatemia Absence of hypercalcemia usually speaks against the diagnosis of Recklinghausen's disease, although, as previously mentioned, cases of hyperparathyroidism may, on rare occasions, pass through periods in which hypercalcemia is not pronounced or is absent In hyperparathyroidism, hypophosphatemia is also fairly constant, in xanthomatosis ossium, the inorganic phosphorus of the serum is usually not reduced

5 Phosphatase In hyperparathyroidism the phosphatase of the plasma is increased to many times the normal value, in xanthomatosis, it is normal or but slightly increased In our patient it was 84 units, the average normal for his age being 5 units

6 Cholesteremia Hypercholesteremia may be present in xanthomatosis The increase may be more marked in the cholesterol esters than in the free cholesterol

7 Hypercalcemia test in the rabbit Hamilton and Schwartz<sup>35</sup> recently reported a test for the presence of a parathyroid hormone in the blood This consists of determining the rise in the levels of serum calcium in a rabbit which has been given a definite amount of calcium chloride by stomach tube and which has received intramuscular injections of the blood to be tested In hyperparathyroidism, the curve is much higher than normal, it may be compared to standard curves obtained by injecting graded amounts of parathyroid hormone and the same amount of calcium

8 Calcium and phosphorus metabolism In typical cases of osteitis fibrosa cystica, the constant abstraction of calcium from the bones produces a calciuria, so that when the patient is placed on a low calcium diet (100 to 200 mg daily) the excretion of calcium in the urine usually exceeds many times the intake In our patient, the results of such a test diet were entirely normal

9 Biopsy In Recklinghausen's disease, the introduction of a curet into a cystic area meets with no resistance, as if the instrument had passed into a cavity, while in xanthomatosis, the areas which appear cystlike in the roentgenograms may offer some resistance to the insertion of the curet, since these pseudocystic areas are composed of fibrous or sclerotic tissue rather than of necrotic or degenerated material

10 Histologic appearance The histologic appearance of the bones from patients with xanthomatosis ossium resembles closely that of osteitis fibrosa, and for this reason xanthomatosis may be easily mis-

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35 Hamilton, B, and Schwartz, C Rickets and Hyperparathyroidism, *Am J Dis Child* 46 775 (Oct) 1933

taken for the latter disease. Therefore, in every case showing dystrophy of the osseous system, especially without hypercalcemia, the biopsy material should be stained for lipoids, in order to establish or rule out the diagnosis of lipoid granulomatosis.

11. Course. In most cases of osteitis fibrosa the condition does not improve spontaneously, whereas in the three cases reported by Kienbock and Meworach, Snapper and Parisel and ourselves, the disease process came to a standstill without resort to parathyroidectomy.

In addition to osteitis fibrosa cystica, xanthomatosis ossium may easily be confused with melanoma, multiple myeloma, tuberculosis, syphilis, osteomyelitis and metastatic infiltrations of tumor cells. In melanoma and in multiple myeloma, Bence-Jones' protein is noted in the urine, but this finding is by no means confined to these maladies. Bence-Jones' albuminuria may be present in other diseases not involving the skeletal system, or even in xanthomatosis, as occurred in Gilmore's patient.<sup>36</sup> Multiple tuberculous lesions of the bones are usually associated with tuberculous infections elsewhere in the body, the tuberculin test is positive, and there is a tendency to formation of sinuses. In syphilis, the Wassermann reaction is positive, other syphilitic manifestations may be present, and the lesions usually respond fairly promptly to antisyphilitic therapy. In acute osteomyelitis, there are fever and pain, and in the chronic form there is a tendency to sinus formation and the breakdown of tissues. Leukemia and Hodgkin's disease, involving the skeletal system, may occasionally simulate roentgenologically osteitis fibrosa or xanthomatosis. In these instances, a careful study of the blood cells and the presence of an enlarged spleen or of a generalized adenopathy usually reveals the true nature of the disease. Metastatic infiltrations from the thyroid, bronchi, stomach, breast, suprarenals or prostate should always be ruled out by careful physical examination. The age of the patient is of some diagnostic significance. Lipoid granulomatosis is more common in children and young adults, while neoplastic infiltrations are prevalent in older persons. A biopsy usually aids in ascertaining the correct diagnosis.

Xanthomatosis ossium must also be differentiated from other forms of lipoid granulomatosis, such as Gaucher's disease and Niemann-Pick's disease. In these diseases, the infiltrations are usually not limited to the bones, the liver and spleen being nearly always enlarged. Niemann-Pick's disease occurs in infancy and early childhood and is particularly frequent among Jews. The lipoid in Gaucher's disease is composed largely of lecithin, and in Niemann-Pick's disease, of kerasin, as against the predominance of cholesterol in xanthomatosis ossium or in Schuller-Christian's syndrome.

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<sup>36</sup> Gilmore, M. E. *Texas State J. Med.* **21** 358, 1925.

No special therapy was instituted in the case of our patient. He received a balanced diet and frequent exposures to ultraviolet radiation. His general condition at present is stationary, and if the lesions do not improve spontaneously, high voltage roentgenotherapy will be tried on the basis of the beneficial results obtained locally with this form of therapy in Schuller-Christian's disease.<sup>8</sup>

#### SUMMARY

A case of generalized xanthomatosis, or lipoid granulomatosis of the bones, is described, in which the roentgenograms and histologic sections of biopsy material strongly suggested osteitis fibrosa cystica. The correct diagnosis was finally made by observing foam cells in some of the sections, by staining freshly removed material from the bone for lipoid and by finding a normal calcium balance.

The factors in the differential diagnosis of xanthomatosis ossium, osteitis fibrosa and other dystrophies of the skeletal system are enumerated and discussed.

# HEART DISEASE IN PATIENTS WITH UTERINE MYOMA

A CLINICAL STUDY OF FIFTY CASES

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The question as to whether or not uterine myoma causes heart disease has been argued since 1885 when Hofmeier<sup>1</sup> started the discussion by saying that he believed this type of tumor could injure the heart. Most of the early writers agreed with Hofmeier, although in 1890 Williams<sup>2</sup> expressed a contrary opinion when he said that in his experience, uterine fibroid was less often associated with heart disease than was any other pelvic lesion. Strassmann and Lehmann<sup>3</sup> in 1898 reported a series of 71 cases of uterine myoma in 34 per cent of which there was evidence of cardiac damage. These authors believed that the tumor could cause degenerative changes in the heart muscle. Other early writers who agreed with the views of Strassmann and Lehmann were Wilson,<sup>4</sup> Fleck,<sup>5</sup> Baldy,<sup>6</sup> Cumston,<sup>7</sup> Boldt<sup>8</sup> and Kessler<sup>9</sup>. The

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From the Departments of Gynecology and Medicine, Philadelphia General Hospital

Read before the section on General Medicine of the College of Physicians, Philadelphia, April 23, 1934

1 Hofmeier, M. Zur Lehre vom Shock (Ueber Erkrankungen der Circulationsorgane bei Unterleibsgeschwulsten), *Ztschr f Geburtsh u Gynak* **11** 366, 1885

2 Williams, J. D. The Co-Existence of Heart Disease and Pelvic Lesions, *Edinburgh M J* **36** 440 (Nov) 1890

3 Strassmann, P., and Lehmann, F. Zur Pathologie der Myomerkkrankung, *Ztschr f Geburtsh u Gynak* **38** 111, 1898

4 Wilson, Thomas. The Relation of Organic Affections of the Heart to Fibromyoma of the Uterus, *Tr Obst Soc London* **42** 176 (May 2) 1900, *The Cardiopathy of Uterine Fibromyoma*, *J Obst & Gynaec Brit Emp* **6** 107 (Aug) 1904

5 Fleck, Georg. Myom und Herzerkrankung in ihren genetischen Beziehungen, *Arch f Gynak* **71** 258, 1904

6 Baldy, J. M. The Mortality in Operations upon Fibroid Tumors of the Uterus, *Am J Obst* **52** 370 (Sept) 1905

7 Cumston, C. G. Cardiac Disease and Uterine Fibromyomata, *New York M J* **82** 893 (Oct 28) 1905

8 Boldt, H. J. Uterine Myofibromata and Visceral Degeneration, *New York M J* **82** 887 (Oct 28) 1905

9 Kessler, L. Myom-Herz-Ovarium, *St Petersburg med Wchnschr* **22** 421 (Oct 8) 1905

question as to whether secondary anemia from menorrhagia and metrorrhagia in these cases was not an important factor in producing cardiac symptoms was brought out early in the course of the discussion. However, Brasin<sup>10</sup> in 1893 discounted the importance of secondary anemia by pointing out that heart disease was less common in patients with carcinoma of the uterus and secondary anemia from hemorrhage than it was in patients with uterine myoma and secondary anemia.

Early authors who were not convinced that uterine myoma per se could cause heart disease were von Rosthon,<sup>11</sup> Winter<sup>12</sup> and Neu.<sup>13</sup> The latter was of the opinion that it was not logical to consider every cardiac disturbance occurring in a patient with a fibroid as being caused by a fibroid heart. He believed that the conception of the fibroid heart was not tenable, as proof of its existence was lacking. McGlynn<sup>14</sup> in 1914 reported the results of a study of 131 cadavers in which uterine myoma was found. He compared the cardiac findings at necropsy with the cardiac findings in a similar number of persons of the same age and sex in whom a tumor was not present. He reached the conclusion that the conception of a fibroid heart cannot be sustained, that uterine myoma is often associated with sclerotic lesions of the heart although it is not a cause of these lesions and that anemia resulting from hemorrhage from the tumor can affect the heart secondarily.

In the meantime other American authors were expressing their belief in the existence of an abnormal condition of the heart caused by myoma as a definite entity. Payne<sup>15</sup> in 1911 said that he believed that cardiac symptoms in patients with myoma are due not to secondary anemia but to the action of products of the uterine growth on the heart muscle. These views were concurred with by Doane<sup>16</sup> and by Barrows.<sup>17</sup> Several years later, beginning in 1921, various authors began to note a causal relationship between uterine myoma and arterial hypertension.

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10 Brasin, cited by Kessler<sup>9</sup>

11 von Rosthon, cited by Brickner, S. *Am J Obst* **62** 1027 (Dec.) 1910

12 Winter, G. *Die wissenschaftliche Begründung der Indikationen zur Myomoperation*, *Ztschr f Geburtsh u Gynak* **55** 49, 1905

13 Neu, M. *Ueber die Beziehungen zwischen Herz und Myom*, *Ztschr f Geburtsh u Gynak* **66** 688, 1910

14 McGlynn, J. A. *The Heart in Fibroid Tumors of the Uterus*, *Surg, Gynec & Obst* **18** 180 (Feb.) 1914

15 Payne, R. L., Jr. *The Surgical Relationship Between Uterine Fibroids and Loss of Cardiac Compensation*, *J A M A* **56** 1324 (May 6) 1911

16 Doane, P. S. *Cardiac Changes Secondary to Uterine Myomata*, *Surg, Gynec & Obst* **14** 42 (Jan.) 1912

17 Barrows, C. C. *The Myoma Heart*, *Am J Surg* **26** 161 (May) 1912

Vaquez and Leconte,<sup>18</sup> Heitz,<sup>19</sup> Muller<sup>20</sup> and later Vassitch<sup>21</sup> were among those who wrote on the subject. These views were partially confirmed by Alvarez and Zimmerman,<sup>22</sup> who found that the blood pressure of women with uterine myoma was higher than that of women of the same age without such a tumor, particularly among those in the fifth decade. However, they felt that the increased blood pressure and the uterine tumor were both a result of some underlying diathesis rather than that the tumor caused the increased blood pressure. Opposed to this view of a relationship between uterine myoma and hypertension was that expressed by Polak, Mittell and McGrath<sup>23</sup> who, in studying 416 patients with a uterine fibroid decided that there was no effect on the blood pressure attributable to the tumor in young women and that patients with uterine myoma who had high blood pressure were usually over 40 years of age, at which age the hypertension could be attributed to other causes.

The controversy continued. In 1924 Winter<sup>24</sup> again expressed his opinion that there was no evidence in favor of a cardiac lesion produced by uterine myoma alone and occurring only with uterine myoma. Strassmann<sup>25</sup> in 1925 decided that both uterine myoma and the cardiovascular damage that he found so often associated with it were caused by a dysfunction of the ovaries. This theory has not been confirmed. Brandman<sup>26</sup> in 1932 reported the case of a patient with severe secondary anemia due to uterine bleeding from a fibroid who was in a state of cardiac decompensation. Treatment of the anemia and removal of the tumor resulted in a return of compensation and a decrease in the size of the heart. Brandman stated that the only effect that a fibroid can have on the heart is a secondary one due to anemia.

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18 Vaquez, H, and Leconte. Le passe, le present et l'avenir des hypertendus, *Paris med* **2** 11 (July 2) 1921

19 Heitz, J. Hypertension et fibromes uterins, *Bull Acad de med, Paris* **87** 422 (April 18) 1922

20 Muller, F. Die Bedeutung des Blutdruckes fur den practischen Arzt, *Munchen med Wchnschr* **70** 1 (Jan 5) 1923

21 Vassitch, M. Les fibromes uterins et l'hypertension arterielle, *Gynec et obst* **24** 126 (Aug) 1931

22 Alvarez, W C, and Zimmerman, A. Blood Pressure in Women as Influenced by the Sexual Organs, *Arch Int Med* **37** 597 (May) 1926

23 Polak, J O, Mittell, E A, and McGrath, A B. What Is the Relation of Hypertension to Fibroid Disease of the Uterus? *Am J Obst & Gynec* **4** 227 (Sept) 1922

24 Winter, G. Myom und Herz, *Ztschr f Geburtsh u Gynak* **87** 225, 1924

25 Strassmann, E. Die Kreislaufanderung durch Klimakterium und Kastration, besonders bei Myom, *Arch f Gynak* **126** 169, 1925

26 Brandman, H. Fibromyoma of the Uterus, Cardiac Failure, Anemia and Edema, *Arch Int Med* **50** 306 (Aug) 1932



The authors of textbooks on gynecology are still somewhat divided in their opinions on the question. Anspach<sup>27</sup> expressed the opinion that in patients with myoma around middle life arteriosclerosis is to be looked on as an associated lesion and not as a lesion produced by the myoma. Graves<sup>28</sup> in the 1928 edition of his "Gynecology" said that it is well to reserve judgment on the matter until the facts are better established. However, the same author writing in 1933 in Curtis' "Obstetrics and Gynecology"<sup>29</sup> decided that aside from functional changes that result from long-standing secondary anemia uterine myoma has no specific degenerative influence on the heart. The Crossens<sup>30</sup> were at least convinced that heart disease is present in a large percentage of patients with myoma. In the last edition of "Diseases of Women" it is stated that whether "the heart disturbances are due principally to chronic anemia from hemorrhage or to the direct action of some toxin produced in the myoma or constitute simply an associated product of the same condition that produced the myoma whatever the cause the fact remains that they are there and must be reckoned with." The Crossens summarized five series of cases of fibroid, there being a total of 951 patients, heart disease was present in 38 per cent of the total number, with a variation of from 25 to 47 per cent in the individual series. Fishberg<sup>31</sup> in his book on hypertension and nephritis expressed the same opinion as did the Crossens that cardiac manifestations in patients with uterine myoma are too frequent to be accidental. He did not look on the disturbances of the heart associated with myoma as a unitary concept, however, but said that the cardiac damage is due sometimes to anemia, sometimes to hyperthyroidism accompanying the myoma and sometimes to hypertension. Fishberg said "The nature of the relation between fibroids and arterial hypertension, if any, is not clear."

In order to determine the incidence of cardiovascular damage in patients with uterine myoma and to decide whether or not there is such a clinical entity as the "myoma heart," 50 patients operated on consecutively for uterine myoma in the gynecological department of the Philadelphia General Hospital were studied thoroughly from a cardiovascular point of view. These patients were admitted to the hospital between October 1932 and August 1933. Only those patients operated

27 Anspach, Brooke M. Gynecology, ed 3, Philadelphia, J. B. Lippincott Company, 1927, p. 303.

28 Graves, William P. Gynecology, ed 4, Philadelphia, W. B. Saunders Company, 1928, p. 144.

29 Curtis, Arthur H. Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol 2, p. 779.

30 Crossen, H. S., and Crossen, R. J. Diseases of Women, ed 7, St. Louis, C. V. Mosby Company, 1930, p. 570.

31 Fishberg, Arthur M. Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934, p. 520.

on were included in this series, so that there could be no question as to the correctness of the diagnosis. A few patients refused to permit surgical intervention, and for some it was not indicated. However, in none of the patients admitted and not operated on was cardiovascular disease a contraindication to operation.

#### METHOD OF STUDY

The patient's history was investigated minutely. Possible etiologic factors in the production of heart disease, such as syphilis, scarlet fever, diphtheria and rheumatic infections including sore throat, growing pains and chorea, were sought. Symptoms of cardiac disability, such as shortness of breath, swelling of the ankles, precordial pain and palpitation, were inquired about. A careful examination of the heart and peripheral arteries was made, including the effect of exercise on the blood pressure and the pulse rate. The eyegrounds were studied by an ophthalmologist. Other organs which might show the effect of cardiovascular disability, such as the lungs and the liver and the extremities, were included in the examination. The following special examinations were made: roentgenographic or fluoroscopic examination of the heart, either by means of a plate taken at 6 feet (182.8 cm) or by an orthodiagram, electrocardiography, urinalysis, test for urea clearance, blood count, the Kahn or Wassermann test of the blood, and determination of the blood urea nitrogen. After the operation and before the patient left the hospital the heart was reexamined. If abnormalities were found in the pre-operative electrocardiogram or orthodiagram, the examinations were repeated. From five to six months after the operation as many of the patients were reexamined as was possible, at which time electrocardiograms and orthodiagrams of those who had shown abnormalities were repeated. It was impossible to make the follow-up examination on 13 of the 50 patients, as they could not be found or would not come back to the hospital. Of the 13 patients not reexamined, 9 had normal cardiovascular systems, so only 4 patients with cardiac abnormalities were not studied in the follow-up.

#### OBSERVATIONS

*Age and Race Distribution and Etiologic Factors*—The youngest patient was 26 years old, the oldest was 54. The distribution of the patients according to age and race is given in table 1. Table 2 shows the number of patients for whom the history of an etiologic factor or factors that could cause cardiovascular disability was found. Of the 2 patients with a history of rheumatism, 1 had had an attack of rheumatic fever, and the other gave a history of frequent sore throat and had typical rheumatic mitral valvulitis. Included among those having a history of syphilis are the patients who had a positive reaction of the blood to the Kahn or Wassermann test as well as those with a known history of antisyphilitic treatment. If the history was merely that of symptoms that might be due to syphilis, this was thought too indefinite to make a positive syphilitic history. In none of the patients who had had scarlet fever or diphtheria were these infections a cause of the existing heart disease. Both patients with a history of scarlet fever and 2 of the patients with a history of diphtheria had a normal heart.

Of the other 2 patients with a history of diphtheria, 1 had rheumatic heart disease and the other had hypertensive heart disease

*Symptoms Referable to the Cardiovascular System*—The evaluation of such symptoms as shortness of breath on exertion and swelling of the ankles as evidence of cardiac disability is difficult in the case of a patient with an abdominal tumor, as the tumor can easily produce such symptoms when no real cardiac damage is present. Shortness of breath was complained of by 13 patients (26 per cent). In 9 of the 13 the diagnosis of heart disease was subsequently made, in the other 4 no evidence of cardiovascular damage could be found in the physical or laboratory examinations. The dyspnea on exertion was therefore attributed to the presence of the tumor, which in all of these patients was

TABLE 1—*Distribution According to Age and Race of the Entire Group*

Age, Years	Number of Patients		
	White	Negro	Total
20 to 29	0	7	7
30 to 39	0	27	27
40 to 49	3	11	14
50 to 59	1	1	2
Total	4	46	50

TABLE 2—*Incidence of Possible Etiologic Factors Producing Heart Disease*

Etiologic Factors	Number of Cases	Percentage of
		Total Cases
Rheumatic infection (including all rheumatic manifestations)	2	4
Syphilis	18	36
Scarlet fever	2	4
Diphtheria	4	8

fairly large, averaging the size of a uterus which is three months pregnant. Three of these 4 patients were reexamined six months after the removal of the tumor, and in each case the dyspnea had practically disappeared. Swelling of the ankles toward evening was complained of by 7 patients (14 per cent). Six of these 7 were subsequently shown to have heart disease. In the other patient the edema of the ankles was attributed to the presence of the tumor. The subjective sensation of palpitation, usually in association with shortness of breath, was mentioned by 10 patients (20 per cent). All but 2 of these proved to have cardiac damage. No patient had precordial pain of the anginal type, only 1 patient had definite cardiac pain, and this was 1 of those who had a rheumatic lesion of a valve.

*Cardiac Murmurs and Abnormal Sounds*—Accentuated Aortic Second Sound. Eight of the 50 patients had definite accentuation of the aortic second sound. Hypertension or aortitis or both were present, so that an explanation of this observation on the basis of pathologic change in the cardiovascular system was possible.

**Systolic Murmur at the Apex** Thirteen of the 50 patients had this type of murmur. In 6 of them hypertension and cardiac hypertrophy were present, so it was believed that the murmur was evidence of relative mitral regurgitation. Two of the patients had a history of rheumatic infection, so the murmur was taken as evidence of rheumatic mitral valvulitis. In 1 of the 13 patients definite secondary anemia was present, so the murmur was considered to be hemic. For the 4 patients remaining no explanation of the murmur other than that it was functional could be made. The presence of the murmur alone was not considered evidence of cardiac disease.

**Systolic Murmur at the Aortic Area** Five patients had this type of murmur. In all of these hypertension or aortitis or both were present, so that, as in the case of the accentuated aortic second sound, an explanation of the murmur on a pathologic basis was possible.

**Other Murmurs** One patient with a systolic murmur at the aortic area had a diastolic murmur, heard best at the aortic area and transmitted along the left border of the sternum. A diagnosis of aortic regurgitation as well as aortitis was made in this case. One of the rheumatic patients with an apical systolic murmur had also a presystolic murmur at this valve area, a diagnosis of mitral stenosis as well as mitral regurgitation was made in this case.

**Blood Pressure**—A persistent systolic blood pressure reading of more than 140 mm of mercury for patients under 40 years of age and of more than 150 mm of mercury for patients over 40 years of age was considered abnormally high, and a persistent diastolic blood pressure reading of more than 90 mm of mercury at any age was considered abnormal. These are the standards described by Gager<sup>32</sup> in his book on hypertension. On this basis, 34 of the 50 patients had normal blood pressure. The other 16 had hypertension.

**Sclerosis of the Peripheral Arteries**—Thirty-five of the 50 patients had no palpable thickening of the radial arteries. The other 15 patients showed slight palpable sclerosis of these arteries, and 13 of the 15 had either hypertension or other signs of cardiovascular damage. The other 2 patients had no other signs of cardiovascular disease. This slight deviation from the normal in these patients, both of whom were over 40 years of age, was not thought sufficient to consider them as having cardiovascular disease.

**Changes of the Eyegrounds**—Five of the 50 patients showed vascular changes in the fundus of the eye. One of these was a patient with chronic glomerulonephritis in whom retinal arteriolosclerosis without hemorrhages or exudates was found. The other 4 patients, who also showed arteriolosclerosis, were all in the hypertensive group.

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<sup>32</sup> Gager, Leshe T. Hypertension, Baltimore, Williams & Wilkins Company, 1930, p. 49.

*Roentgen Measurement of the Size of the Heart*—A cardiothoracic ratio greater than 1.2 was considered abnormal. On this basis 37 of the 50 patients showed no enlargement of the cardiac silhouette, and 12 of the remaining 13 showed enlargement of the transverse diameter of the heart or widening of the aorta, or both. The last of the 13 patients showed widening and tortuosity of the aorta without cardiac enlargement. In all the 13 patients hypertension, aortitis or a lesion of a valve was present to account for the abnormal silhouette.

*Electrocardiographic Changes*—Electrocardiograms that showed left axis deviation or inversion of the T wave in lead III or both were not considered abnormal. The presence of occasional extrasystoles was also not considered abnormal.

Prominent Q Wave in Lead III Followed by an Inverted T<sub>3</sub>. This electrocardiographic abnormality occurred in 2 patients before operation.

TABLE 3—*Distribution According to Age and Race of the Patients with Hypertension*

Age, Years	Number of Patients		
	White	Negro	Total
20 to 29	0	0	0
30 to 39	0	5	5
40 to 49	2	7	9
50 to 59	1	1	2
Total	3	13	16

In both of these cases electrocardiograms taken after hysterectomy showed that the Q wave had disappeared. No other evidence of cardiovascular abnormality was found in these patients.

Changes in the T Waves in Leads I or II. Ten patients showed abnormalities of the T waves in lead I or II. The electrocardiograms of 3 patients showed either flattening or partial inversion of the T wave in lead I. In 2 of these, the change in the T wave persisted in the follow-up examination. One of these 2 patients was in the group with hypertension and the other had rheumatic mitral valvulitis. The patient in whom the change in the T wave did not persist showed no cardiac abnormality besides the electrocardiographic change. This will be discussed in detail farther on, along with the changes in the Q wave previously described.

Seven patients showed either flattening or inversion of the T wave in lead II, associated with inversion of T<sub>3</sub>. In 2 of these the follow-up electrocardiogram showed a normal T wave in lead II. In 1 of these 2 patients no other cardiac abnormality had been found, the other was in the group with hypertension. For 1 of these 7 patients a follow-up electrocardiogram could not be obtained. No other cardiac abnormality had been shown in this case. Of the remaining 4 patients, 2 showed lessening of the abnormalities in the T wave in the follow-up exami-

TABLE 4—Significant Cardiac Findings in the Twenty-Free Patients with Evidence of Cardiovascular Abnormalities

Group	Race	Age, Years	Electrocardiogram	Blood Pressure	Cardiac Enlargement	Valvular Lesions	Cardiac Diagnosis
I	Negro	29	T <sub>1</sub> and T <sub>2</sub> flat	150/85	Present	Mitral stenosis and regurgitation	Rheumatic mitral valvulitis
I	Negro	34	Right axis deviation, T <sub>2</sub> and T <sub>3</sub> inverted	130/88	Absent	Mitral regurgitation	Rheumatic mitral valvulitis
II	Negro	34	Normal	132/84	Absent	Aortitis	Syphilitic aortitis
II	Negro	32	Left axis deviation	140 to 158/50 to 70	Present	Aortic regurgitation	Syphilitic aortitis and aortic regurgitation
III	Negro	37	Normal	142 to 160/102 to 124	Absent	None	Chronic glomerulonephritis with hypertension
IV	Negro	37	Left axis deviation	160 to 180/90 to 110	Absent	None	Hypertensive heart disease
IV	Negro	42	Normal	160 to 190/90 to 120	Present	Relative mitral regurgitation	Hypertensive heart disease
IV	White	42	Normal	160 to 180/92 to 118	Present	None	Hypertensive heart disease
IV	White	48	Left axis deviation	160 to 180/94 to 110	Absent	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	39	Left axis deviation	140 to 180/95 to 120	Absent	None	Hypertensive heart disease
IV	Negro	48	Left axis deviation, T <sub>2</sub> and T <sub>3</sub> inverted	186 to 200/92 to 100	Present	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	48	Normal	162 to 174/104 to 118	Present	None	Hypertensive heart disease
IV	Negro	42	Normal	150 to 160/88 to 108	Present	None	Hypertensive heart disease
IV	White	42	Left axis deviation	140 to 172/96 to 100	Absent	Relative mitral regurgitation	Hypertensive heart disease
IV	Negro	43	T <sub>2</sub> and T <sub>3</sub> inverted	176 to 185/95 to 105	Absent	None	Hypertensive heart disease
IV	White	53	Left axis deviation	152 to 180/88 to 100	Present	None	Hypertensive heart disease
IV	Negro	42	Left axis deviation	180/120	Present	Relative mitral regurgitation	Hypertensive heart disease
V	Negro	54	Normal	160 to 180/100 to 110	Present	Aortitis	Hypertensive heart disease syphilitic aortitis
V	Negro	32	Left axis deviation	150 to 180/112 to 130	Present	Aortitis	Hypertensive heart disease, syphilitic aortitis
V	Negro	31	Left axis deviation, T <sub>2</sub> and T <sub>3</sub> inverted	178 to 202/108 to 130	Present	Aortitis, relative mitral regurgitation	Hypertensive heart disease, syphilitic aortitis
VI	Negro	29	Left axis deviation T <sub>2</sub> partly inverted, T <sub>3</sub> inverted, follow up normal	110/ 65	Absent	None	Electrocardiographic changes only
VI	Negro	37	T <sub>1</sub> flat, T <sub>3</sub> inverted, follow up normal	122/ 78	Absent	None	Electrocardiographic changes only
VI	Negro	33	Left axis deviation, T <sub>1</sub> depressed, shading of all ventricular complexes, follow up normal	108/ 70	Absent	None	Electrocardiographic changes only
VI	Negro	29	T <sub>1</sub> partly inverted, T <sub>2</sub> inverted, no follow up	110/ 70	Absent	None	Electrocardiographic changes only
VI	Negro	27	T <sub>2</sub> and T <sub>3</sub> cove shaped, follow up T <sub>2</sub> flat, T <sub>3</sub> inverted	108/ 78	Absent	None	Electrocardiographic changes only

nation, although the wave did not return to normal. Both of these patients showed no other cardiac abnormality besides the electrocardiographic changes, which will be discussed in detail later. In the case of the remaining 2 patients in this group the T wave remained inverted in the follow-up electrocardiogram. One of these had rheumatic heart disease, and the electrocardiogram showed, in addition to the changes in the T wave, right axis deviation, a P wave of increased amplitude and a top-normal P R interval. The other was a patient with hypertension.

*Urea Clearance Test and Determination of Blood Urea Nitrogen—*

A maximum urea clearance of from 80 to 125 per cent and a standard clearance of from 76 to 120 per cent were considered normal. On the basis of this test, 2 of the 50 patients showed a definite impairment of renal function. One showed 32 and 36 per cent standard clearance and the other, 25 and 27 per cent standard clearance for two one hour periods. In both of these patients the concentration of blood urea

TABLE 5—*Incidence of the Various Types of Heart Disease*

Group	Type of Heart Disease	Number of Patients	Percentage of Cardiac Patients	Percentage of All Patients
I	Rheumatic	2	8	4
II	Syphilitic	2	8	4
III	Nephritic	1	4	2
IV	Hypertensive	12	48	24
V	Hypertensive, syphilitic	3	12	6
VI	Electrocardiographic changes only	5	20	10
	Total	25	100	50

nitrogen was slightly elevated (20 mg and 25 mg per hundred cubic centimeters, respectively). One had hypertension, the other did not, and neither had cardiac enlargement. A diagnosis of chronic glomerulonephritis was made in both cases.

*Blood Count*—Only 1 of the patients had marked secondary anemia, i. e., a hemoglobin content below 60 per cent and a red blood cell count below 3,300,000. In this case the hemoglobin content was 50 per cent, and the red blood cell count was 2,820,000.

*Size of the Tumor*—There was no relationship between the existence of heart disease and the size of the uterine myoma. The tumors varied in size from a mass 6 by 4 by 4 cm. to one the size of a uterus six months pregnant.

*Deaths*—One patient died three months after the operation. She was a Negress 43 years of age with hypertensive heart disease and died of cerebral thrombosis. Autopsy was not performed.

*Summary of All Cases*—Of the 50 patients exactly one-half showed no cardiovascular abnormality. Table 4 is a tabulation of the significant cardiac findings in the other 25 patients. These patients are divided into six groups, as shown in table 5.

## COMMENT

*Anemia and Heart Disease*—Secondary anemia due to hemorrhage from uterine myoma is considered an important factor in producing cardiac abnormalities in patients with myoma. However, in this series of 50 patients there was only 1 with anemia. She had an apical systolic murmur but no other evidence of cardiac damage. The murmur was therefore considered hemic, and she was thought to have a normal heart. Both the murmur and the anemia had disappeared six months after the operation.

*Heart Disease Other than Hypertension*—The cardiac damage of the patients in groups I, II and III had obvious etiologic factors, that is, rheumatic infection, syphilis and chronic glomerulonephritis. The uterine myoma in these patients was obviously a coexisting lesion that had nothing to do with the production of heart disease.

*Hypertension and Uterine Myoma*—The patients in groups IV and V, with hypertensive cardiovascular disease and uterine myoma, need a more detailed consideration. Those in group V had syphilitic aortitis as well as hypertension. That this combination is not uncommon was pointed out by Fishberg,<sup>33</sup> who showed also that there is no reason to believe that the syphilitic infection causes the hypertension.

If uterine myoma has any effect on the cardiovascular system (aside from that due to anemia), it either produces hypertension or is associated with an increased incidence of hypertension. The literature on this question has already been discussed. To decide whether this study indicates a relationship between uterine myoma and hypertension, it must be determined whether there is a greater incidence of hypertensive cardiovascular disease in our patients with uterine myoma than in other women of the same age and race.

Gage,<sup>32</sup> in a study of the incidence of essential hypertension in 1,000 women in the clinic of the Cornell Medical Center, New York, found the incidence by ten year periods to be as shown in table 6.

Patients with hypertension associated with aortic regurgitation or with glomerulonephritis were not included in this table. Gage's standards for increase in blood pressure have already been given. He did not state what proportion of the patients were Negro. An interesting and significant fact brought out by this study is that there is a sharp rise in the incidence of hypertension in women beginning at the age of 40, while in men this rise does not begin until a decade later. Risemann and Weiss<sup>34</sup> had previously made the same observation.

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<sup>33</sup> Fishberg,<sup>31</sup> p. 542.

<sup>34</sup> Risemann, J. E. F., and Weiss, Soma. The Age and Sex Incidence of Arterial Hypertension, *Am. Heart J.* 5: 177 (Dec.) 1929.



Studies by various authors<sup>35</sup> on the relative incidence of hypertensive heart disease in Negroes and in white persons have shown that this type of heart disease is much more common in Negroes. In Stone and Vanzant's<sup>35b</sup> series, hypertensive heart disease was found twice as often in Negroes as in white persons, and in Schwab and Schulze's<sup>35c</sup> series the incidence was two and a half times greater. All of these investigators agreed that this type of heart disease begins earlier in Negroes and that its onset is especially early in Negro women.

We are safe in assuming that less than one third of the patients in Gager's series of patients were colored, as even in the southern clinics

TABLE 6—Gager's Figures on the Percentage of Incidence of Essential Hypertension

Age, Years	Patients with Systolic Hypertension	Patients with Diastolic Hypertension
20 to 29	3.9	3.4
30 to 39	11.6	8.9
40 to 49	22.2	27.0
50 to 59	36.7	31.5

TABLE 7—Incidence of Hypertension in This Series Compared with That in Gager's Series<sup>\*</sup>

Age, Years	Total Number of Patients		Number with Hypertension		Percentage Incidence of Hypertension		Gager's Figures of Percentage Incidence of Systolic Hypertension
	White	Negro	White	Negro	White	Negro	
20 to 29	0	7	0	0	0	0	3.9
30 to 39	0	27	0	4	0	14.8	11.6
40 to 49	3	11	2	7	66.7	63.6	22.2
50 to 59	1	1	1	1	100.0	100.0	36.7

\* The patient with nephritic hypertension is not included.

the ratio of white people to Negroes is about 2:1. The incidence of hypertensive heart disease in patients of this series in the 20 to 29 year group, in which no hypertension was found, is obviously less than in Gager's series. Its incidence in the 27 Negro patients in the 30 to 39 year group was lower than one might expect from Gager's figure for this decade, considering that this type of heart disease is at least twice as common in Negroes as in white people. In other words, the incidence of hypertensive heart disease in the patients with myoma under 40

35 (a) Wood, J. E., Jones, T. D., and Kimbrough, R. D. The Etiology of Heart Disease, *Am J M Sc* **172** 185 (Aug.) 1926. (b) Stone, C. T., and Vanzant, F. R. Heart Disease as Seen in a Southern Clinic, *J A M A* **89** 1473 (Oct. 29) 1927. (c) Schwab, E. H., and Schulze, V. E. The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary, *Am Heart J* **7** 223 (Dec.) 1931. (d) Laws, C. L. The Etiology of Heart Disease in Whites and Negroes in Tennessee, *ibid* **8** 608 (June) 1933.

years of age is no greater, indeed probably less, than its general incidence in women of the same age and race

For the patients over 40 years of age this statement is not true. The incidence of hypertensive Negro patients in the fifth decade in this series is higher than in Gager's series, even if one assumes that all of Gager's patients were white and that hypertension is two and a half times as frequent in the Negro as in the white race. The incidence of hypertension in the white patients in this series and in the patients over 50 years of either race is, of course, much higher than in Gager's series. The number of patients over 40 years of age (16) is however, small as compared with the number of patients under 40 years (34), so that one must be careful in drawing conclusions about the older patients. It is significant that of the 12 patients with hypertension who were reexamined, from a total of 15, none showed a decrease in the blood pressure or a decrease in the size of the cardiac silhouette (if enlargement had been present before). In fact, in 3 of these patients the blood pressure was definitely higher at the follow-up examination than it had been before the operation. This increase may have been due to the production of an artificial menopause, but in any case it tends to disprove a causal relationship between the tumor and the hypertension.

The incidence of hypertension in the patients with myoma under 40 years of age is no higher than its general incidence in women of the same age and race. Thus there does not appear to be any connection between uterine myoma and hypertensive heart disease in women of this age. The increased incidence of hypertension in the patients in the fifth and sixth decades may indicate a possible connection in this age period. However, if there were any causal relationship between uterine myoma and hypertensive heart disease it ought to be evident before as well as after the age of 40. A larger number of women in the older age group must be studied before definite conclusions can be drawn.

*Electrocardiographic Changes in Patients with Uterine Myoma*—It has already been said that the preoperative electrocardiograms of 2 of the patients showed a prominent Q wave in lead III followed by an inverted T wave. The postoperative electrocardiograms were normal, and no other evidence of cardiac disease was obtained. Figure 1 shows the preoperative and postoperative electrocardiograms for 1 of these patients. It was believed that the diaphragm made high by increased intra-abdominal pressure as a result of the tumor was responsible for these changes. Pardee<sup>36</sup> has reported, in the case of a pregnant woman, similar electrocardiographic changes which disappeared after delivery.

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<sup>36</sup> Pardee, Harold, E. D. The Significance of an Electrocardiogram with a Large Q in Lead III, *Arch. Int. Med.* 46:470 (Sept.) 1930.

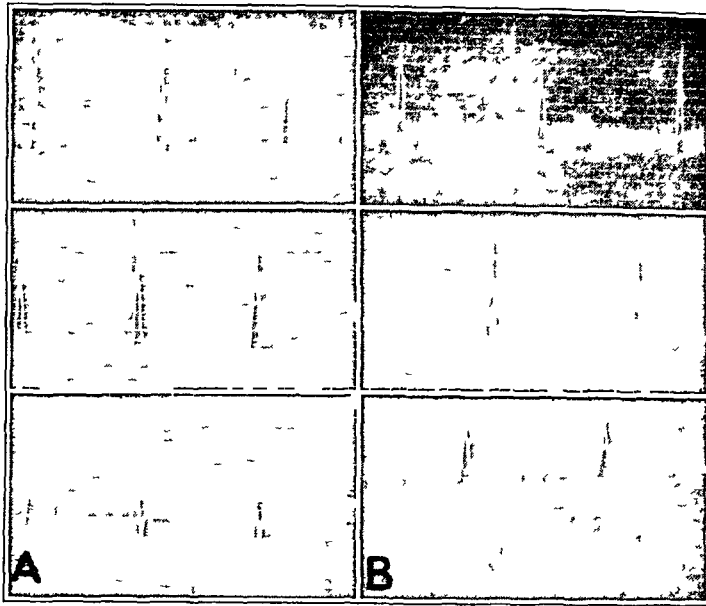


Fig 1—*A* is the preoperative electrocardiogram of patient 11 made on Nov 2, 1932, showing a prominent Q wave in lead III followed by an inverted  $T_s$  wave. The operation was performed on November 8. *B* is the electrocardiogram of the same patient made on Nov 28, 1932, showing a return to normal.

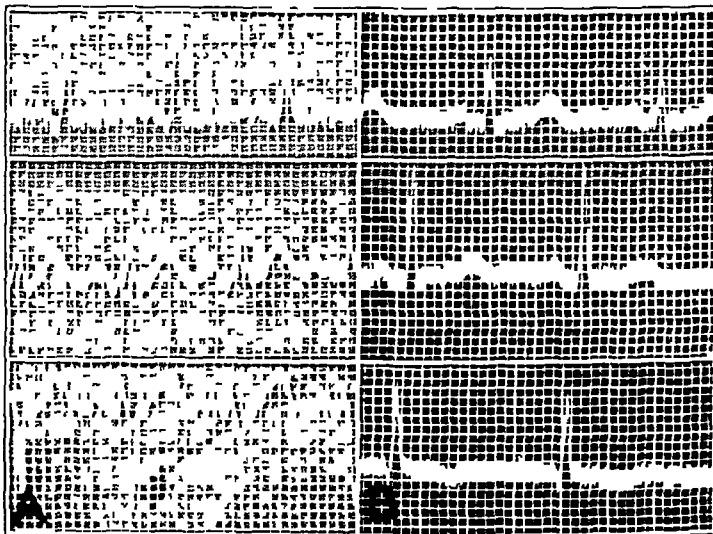


Fig 2—*A* is the preoperative electrocardiogram of patient 18 made on Jan 14, 1933, showing the slurred QRS complex in lead II and a depression of the T wave in lead I. The operation was performed on January 16. *B* is the electrocardiogram of the same patient made on June 15, showing a return to normal.

The electrocardiographic changes presented by the 5 patients of group VI (table 5) who showed no other evidence of cardiac damage are more difficult to explain. In the electrocardiograms of 2 of these patients the T wave had returned to normal in the follow-up examination. The electrocardiogram of 1 of these showed, before operation partial inversion of the T wave in lead II associated with the inversion of  $T_3$  and left axis deviation. After operation the left axis deviation and inverted  $T_3$  remained, but the T wave in lead II was normal. This patient was of hypersthenic habitus with a horizontal type of heart, the width of which was top-normal. The electrocardiogram of the other of these 2 patients showed, before operation, left axis deviation, shading of the ventricular complexes in all leads, and

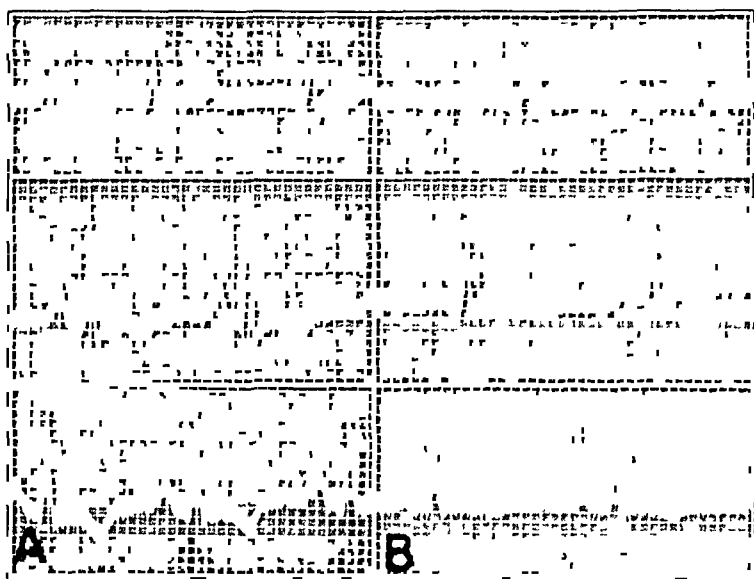


Fig 3—*A* is an electrocardiogram of patient 32, made on April 18, 1933, showing the cove-shaped T wave in leads II and III. The operation was performed on April 21, 1933. *B* is the electrocardiogram of the same patient, made on October 15, showing a flat T wave in lead II and an inverted T wave in lead III.

depression of the T wave in lead I. Six months after operation the electrocardiogram showed a normal condition. Figure 2 shows the pre-operative and postoperative electrocardiogram of this patient. She was obese and the heart was of the horizontal type, although not as markedly so as was that of the record shown in figure 1.

Of the other 3 of the 5 patients, 1 showed before operation partial inversion of the T wave in lead II associated with inversion of  $T_3$ . A follow-up examination could not be obtained. She was obese, with a horizontal type of heart the width of which was top-normal. The remaining 2 patients showed changes in the T wave in lead II that were less marked in the follow-up examination than before the operation, but the wave had not returned to normal. Neither of the patients

was of hypersthenic habitus, and their hearts were not horizontal. The electrocardiogram of 1 of them before operation showed a flat T wave in lead II associated with the inversion of  $T_3$ . Subsequently  $T_2$  became slightly diphasic while  $T_3$  remained inverted. The preoperative electrocardiogram of the other patient showed the cove-shaped type of inversion of the T wave in leads II and III. Six months after the operation the T wave in lead II was flat, while that in lead III was inverted. Figure 3 shows the preoperative and postoperative electrocardiograms of this patient.

It is of course well known that the electrocardiogram is affected by the position of the patient in which the tracing is taken and by the position of the heart in the body. Cohn<sup>37</sup> has studied the effect of change of position of the heart on the electrocardiogram by changing the position of the electrodes on the wall of the chest. He was able to produce not only a change in the axis deviation but also an inversion of the T waves in all leads by this method. In order to produce an inversion of  $T_2$ , he had to rotate the electrodes enough to correspond to a change in the anatomic cardiac angle from a normal of  $+46$  degrees to  $-74$  degrees. To produce the inversion of  $T_1$  and  $T_2$  he had to rotate the electrodes enough to correspond with a cardiac anatomic angle of  $-114$  degrees. In these patients with a fibroid the change in the position of the heart due to the tumor could not have been as much as this. Most of the fibroids were moderate-sized or large, although one was small (7 by 5 by 5 cm), and this was in 1 of the patients in whose electrocardiogram the T wave was normal postoperatively. Thus the electrocardiographic changes do not seem to depend absolutely on the size of the tumor. None of the patients had complete inversion of  $T_1$ . The 2 patients whose T wave returned to normal after the operation had shown only partial inversion of the T wave, and both had the type of heart which goes with a high diaphragm. There is thus some evidence in favor of the view that the abnormalities of the T wave were due not to changes in the cardiac muscle but rather to a change in the position of the heart as a result of the abdominal tumor. The same applies, although not as clearly, to the 2 patients in whose electrocardiograms there was lessening of the abnormality of the T wave without complete return to normal. These 4 cases seem to indicate the possibility that abdominal tumors producing a change in the position of the heart result in alterations of the T wave in leads I and II of the electrocardiogram, although this study does not prove the point. In any case, we cannot consider these electrocardiographic changes occurring in patients with no other evidence of cardiac disease as conclusive evidence of cardiac damage.

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37 Cohn, A. E. An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9 311 (Dec.) 1922

## SUMMARY AND CONCLUSIONS

In a series of 50 patients with uterine myoma 25 (50 per cent of the total) showed evidence of cardiovascular disease

In 5 of these the only evidence of cardiac damage was in the electrocardiogram, consisting of changes in the T wave in leads I and II. The possibility that these electrocardiographic changes were due not to damage of the heart muscle but to change in the position of the heart as a result of the abdominal tumor is pointed out and discussed.

The percentage of patients with heart disease (40), not counting the 5 just mentioned, was found to agree closely with that of five series previously reported, totaling 951 patients with uterine myoma, which showed an average incidence of 38 per cent with a variation of from 25 to 47 per cent in the individual series.

There was no question of secondary anemia from uterine bleeding being a cause of heart disease in this series of patients. Only 1 of the 50 patients was anemic, and she proved to have a normal heart.

In 5 of the 20 patients with definite signs of cardiac disease, obvious etiologic factors other than the uterine myoma were present. In 2 of them the etiologic factor was rheumatic infection, in 2 it was syphilis and in 1 it was chronic glomerulonephritis.

The remaining 15 of the 20 patients had hypertensive heart disease. It is pointed out that it is this type of heart disease, if any, that may have uterine myoma as an etiologic factor.

The incidence of this type of heart disease in the patients of this series under 40 years of age was found to be no higher than its general incidence in women of the same age and race. This study therefore shows no relationship between uterine myoma and hypertension in the third and fourth decades.

The incidence of hypertensive heart disease in the patients in the fifth and sixth decades, however, was found to be higher than its general incidence in women of the same age and race. This might indicate a relationship between the two conditions at this age period. However, because there were relatively few patients in this age group, a larger number of older patients with myoma should be investigated before definite conclusions are drawn.

No indication was found in this study of any such clinical entity as the "myoma heart" in the sense of a type of heart disease caused by and occurring with uterine myoma alone.

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# JUVENILE DEMENTIA PARALYTICA

## II FAMILY HISTORY, WITH SPECIAL CONSIDERATION OF FAMILIAL NEUROSYPHILIS

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This report, the second of a series of studies of juvenile dementia paralytica, is confined to an analysis of the family history, particularly the incidence of syphilis, neurosyphilis and mental disease. A previous report<sup>1</sup> covered the incidence, sex and age at onset. This study is based on 43 cases personally observed and 610 cases recorded in the literature.

### INCIDENCE OF SYPHILIS IN FAMILY

Of the entire series of 653 cases the family history is detailed in 399 and is not given in 254. Syphilis in some form was demonstrated in one or more members of the family in 369 cases. Syphilis was demonstrated clinically or serologically (or both) in the mother in 223 cases, in the father in 226 cases and in one or more of the siblings in 114 cases.

*Syphilis in the Mother* —It is a recognized, established fact that the mother of a syphilitic child is herself syphilitic. Consequently one may correctly assume that maternal syphilis is present in every case of juvenile dementia paralytica. It is of interest, however, to summarize the incidence of maternal syphilis in this series as shown either by clinical or by serologic evidence (or by both). In the 399 cases of juvenile dementia paralytica (in which the family history is recorded), in 223 instances the mother was demonstrated to have syphilis. The types of maternal syphilis are shown in table 1.

Thus syphilis was demonstrated in the mother in 56 per cent of the 399 cases of juvenile dementia paralytica in which the family history is reported. It is certain that in many cases the family, including the mother, was not available for study, and in many reports no mention is made of any investigation as to the family history. Nevertheless, in 34.1 per cent of the entire series of 653 cases of juvenile dementia paralytica, the mother presented either clinical or serologic evidence (or both) of syphilis.

An analysis of table 1 shows three points. 1. Of the 223 instances in which maternal syphilis was demonstrable the patient was male in 59 per cent and female in only 39 per cent.

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From the Menninger Clinic

1 Menninger, W. C. Juvenile Paretic Neurosyphilis Studies. I. Incidence, Sex, and Age at Onset, *Am. J. Syph. & Neurol.* **18**: 486 (Oct.) 1934.

2 The mother had neurosyphilis in 58 cases, representing 26 per cent of all the demonstrable cases of maternal syphilis, this figure does not include possible cases of asymptomatic neurosyphilis since investigation of the spinal fluid was not carried out as a routine. In most instances such an investigation would have been impossible even though considered desirable by the investigator. The inclusion of the asymptomatic cases would increase the percentage of cases of neurosyphilis considerably. But the incidence of neurosyphilis of 26 per cent in the group of 223 mothers is much higher than the incidence in average groups of female patients with syphilis. The incidence of clinical neurosyphilis in syphilis in females was given by Moore<sup>2</sup> as 6.4 per cent, a figure which represents one-fourth the frequency found in the mothers of the patients with juvenile dementia paralytica. It appears that the mothers of neurosyphilitic offspring show a much higher incidence of neurosyphilis than an average group of female syphilitic patients.

TABLE 1—Incidence of Syphilis in the Mother

Type of Syphilis in Mother	Total Number of Cases	Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated
Syphilis without neurosyphilis	165	100	65	0
Dementia paralytica	30	20	10	0
Other forms of neurosyphilis	28	12	13	3
Total	223	132	88	3

3 The table shows approximately an equal distribution of dementia paralytica and other forms of neurosyphilis in the mothers, from this fact one may conclude that there is no female predisposition in the transmission of dementia paralytica.

A more detailed analysis of the 165 cases of maternal syphilis (not including neurosyphilis) is given in table 2 which shows the association of the maternal syphilis with other instances of syphilis or mental disease in the family.

The data presented in table 2 do not permit any significant conclusions, they merely call attention to the frequency of association of demonstrable syphilis in the mother with syphilis and mental disease in other members of the family. In approximately 50 per cent of the cases, some other member of the family besides the mother was demonstrated to have syphilis or mental disease.

*Syphilis in the Father*—In 399 cases of the total series of 653 cases of juvenile dementia paralytica information is given regarding the family history. In these 399 cases the father presented clinical or serologic

2 Moore, J. E. Studies in Asymptomatic Neurosyphilis. III. The Apparent Influence of Pregnancy on the Incidence of Neurosyphilis in Women, Arch Int Med 30: 548 (Nov.) 1922.



evidence (or both) of syphilis in 226 instances, the syphilitic involvement is classified as to type in table 3

Thus paternal syphilis was demonstrated in 56.7 per cent of the 399 cases of juvenile dementia paralytica in which sufficient family his-

TABLE 2—Incidence of Late Stages of Syphilis (Excepting Neurosyphilis) in the Mother \*

Associations with Syphilis or Mental Disease in the Family	Cases in Boys	Cases in Girls	Total Number of Cases
Maternal and paternal syphilis	29	27	56
With mental disease in nonsyphilitic member of family	2♂ 0♀		
With congenital syphilis in one or more offspring	3♂ 5♀		
With paternal neurosyphilis	3♂ 10♀		
With congenital syphilis in offspring and mental disease in nonsyphilitic member in family	1♂ 0♀		
With no data except presence of syphilis in parents	20♂ 12♀		
	29♂ 27♀		
Maternal syphilis (paternal syphilis absent or unknown)	71	38	109
Syphilis in one or more offspring	13♂ 9♀		
Juvenile dementia paralytica	4♂ 1♀		
Syphilis without neurosyphilis	9♂ 8♀		
	13♂ 9♀		
With mental disease in nonsyphilitic member of family	3♂ 1♀		
With syphilis in mother only	55♂ 28♀		
	71♂ 38♀		
Total maternal syphilis (excluding maternal neurosyphilis)	100	65	165

\* In this and in subsequent tables the following terms are used "maternal" and "paternal" refer to the mother and father of the patient with juvenile dementia paralytica "Family" includes brothers or sisters and uncles and aunts of the patient "Offspring" refers to other children with congenital syphilis, brothers or sisters of the patient "Mental disease" includes hypophrenia, neurotic and psychotic illnesses and instances so designated occurring in nonsyphilitic members of the family so far as is known "Siblings" refers to brothers or sisters of the patients with juvenile dementia paralytica

TABLE 3—Incidence of Syphilis in the Father

Type of Syphilis in the Father	Total Number of Cases	Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated
Syphilis without neurosyphilis	146	97	49	0
Dementia paralytica	57	34	23	0
Other forms of neurosyphilis	23	15	2	6
Total	226	146	74	6

tory was recorded. In the entire series of 653 cases paternal syphilis was demonstrated in 34.6 per cent.

An analysis of table 3 reveals further information. In the 226 instances of paternal syphilis the patient was male in 64.6 and female in only 32.7 per cent of the cases. In the entire series of cases surveyed in this study the males represented 57 per cent and the females 43 per cent, these figures, when compared with the percentage of patients

of each sex having a demonstrable paternal syphilitic history, suggest a predisposition of paternal transmission to males. Furthermore, table 3 indicates an incidence of 35.4 per cent of neurosyphilis (in the 226 cases) in the fathers, a figure which again is higher than the average incidence of neurosyphilis in males. The incidence of clinical neurosyphilis in male syphilitic patients was given by Moore<sup>2</sup> as 20.38 per cent, a figure representing nearly half of the incidence of clinical neurosyphilis in the fathers of our patients with dementia paralytica. The figures also show more than twice as frequent occurrence of dementia paralytica as of all other types of neurosyphilis in

TABLE 4—*Occurrence of Late Syphilis (Excluding Neurosyphilis) in the Father*

Associations with Syphilis or Mental Disease in the Family		Cases in Boys	Cases in Girls	Total Num- ber of Cases
Paternal and maternal syphilis		30	19	49
With mental disease in nonsyphilitic member of family	2♂ 0♀			
With congenital syphilis in one or more off- spring	3♂ 5♀			
With maternal neurosyphilis	4♂ 2♀			
With congenitally syphilitic offspring and mental disease in nonsyphilitic member of family	1♂ 0♀			
With no data except presence of syphilis in parents	20♂ 12♀			
	30♂ 19♀			
Paternal syphilis (maternal syphilis absent or unknown)		67	30	97
With congenital syphilis in one or more off- spring	8♂ 6♀			
With congenital neurosyphilis in one offspring	0♂ 3♀			
With mental disease in nonsyphilitic member of family	2♂ 1♀			
With syphilis in father only	57♂ 20♀			
	67♂ 30♀			
Total paternal syphilis (excluding paternal neurosyphilis)		97	49	146

the fathers. This fact suggests a paternal predisposition to transmit dementia paralytica.

A more detailed analysis of the 146 instances of paternal syphilis (excluding neurosyphilis), showing the association of syphilis and mental disease in other members of the family is shown in table 4.

Table 4 again indicates the predominance of the condition in male offspring over that in female children, the ratio being approximately 2 to 1, and these figures are also suggestive of a tendency to predisposition in males. Besides this point there are no obvious conclusions.

*Syphilis in Both Parents*—It was demonstrated either clinically or serologically (or both) that both parents had some form of syphilis in 72 cases. In 19 instances one parent had neurosyphilis, in 6 instances both had dementia paralytica, in 4 instances both had some form of neurosyphilis other than dementia paralytica and in 43 instances both had syphilis without involvement of the central nervous system. The

distribution and further analysis of these cases is presented in table 5. An analysis of this table shows that of 72 cases of juvenile dementia paralytica in which both parents were syphilitic, in 29 (40.3 per cent) at least one parent and in 10 cases (14 per cent) both parents had neurosyphilis. In 9 of these 10 cases, the offspring were male. It is of interest to note that in the 13 cases in which the father had dementia paralytica and the mother had another type of syphilis (not neurosyphilis), the offspring with dementia paralytica was female in 10 instances. Furthermore, 4 of the offspring were male in the 6 instances in which the mother had dementia paralytica and the father had syphilis without involvement of the central nervous system.

TABLE 5—*Syphilis in Both Parents*

Type of Syphilis and Association with Syphilis and Mental Disease in Other Members of Family	Cases in Boys	Cases in Girls	Total Number of Cases
Syphilis, other than neurosyphilis	26	17	43
With one or more congenitally syphilitic offspring	3♂ 5♀		
With congenitally syphilitic offspring and mental disease in nonsyphilitic member of family	1♂ 0♀		
With mental disease in nonsyphilitic member of family	2♂ 0♀		
No data except syphilis in both parents	20♂ 12♀		
	26♂ 17♀		
Neurosyphilis in one or both parents	16	13	29
Neurosyphilis other than dementia paralytica in both parents	3♂ 1♀		
Dementia paralytica in both parents	6♂ 0♀		
Paternal dementia paralytica, maternal syphilis, not neurosyphilis	3♂ 10♀		
Maternal dementia paralytica, paternal syphilis, not neurosyphilis	4♂ 2♀		
	16♂ 13♀		
Total number of patients with both parents with syphilis	42	30	72

*Syphilis in the Siblings*—In the entire series of 653 cases of juvenile dementia paralytica some data were given about the family history in 399 instances. Many of the records, however, did not mention the presence or absence of syphilis in the siblings, even though they contained information regarding the mother and father. This is probably due in part to difficulty in securing contact with other members of the family which was experienced in many of the cases personally observed. In a small percentage of cases the patient was an only child.

Consequently the data on the incidence of syphilis in the brothers and sisters of the patient are probably inadequate. Syphilis was demonstrated in the brothers and sisters of 49 male and of 38 female patients with juvenile dementia paralytica, a total of 87 instances.

A detailed analysis of these 87 cases showing the relationship to different types of parental syphilis and also the occurrence of mental

disease in a nonsyphilitic member of the family is given in table 6. It should be pointed out in the interpretation of this table that the incidence of maternal syphilis includes only the cases with clinical or serologic evidence (or both) of syphilis. Thus in 54 cases of juvenile dementia paralytica with congenital syphilis in brothers and sisters the mother was not reported as being syphilitic though it is an established

TABLE 6—*Incidence of Congenital Syphilis in the Brothers and Sisters*

Associations with Syphilis and Mental Disease in the Family	Cases in Boys	Cases in Girls	Total Num- ber of Cases
Congenital syphilis in brothers and/or sisters and syphilis in both parents	5	7	12
No data except syphilis (not neurosyphilis) in both parents	3♂ 5♀		
Dementia paralytica in mother, syphilis, not neurosyphilis, in father	1♂ 0♀		
Dementia paralytica in father, syphilis, not neurosyphilis, in mother	0♂ 2♀		
No data except both parents with dementia paralytica	1♂ 0♀		
	5♂ 7♀		
Congenital syphilis in brothers and/or sisters and maternal syphilis (paternal syphilis absent or unknown)	10	11	21
Mental disease in nonsyphilitic member of family	0♂ 1♀		
Maternal syphilis, not neurosyphilis	9♂ 8♀		
Maternal dementia paralytica	1♂ 2♀		
	10♂ 11♀		
Congenital syphilis in brothers and/or sisters and paternal syphilis, maternal syphilis absent or unknown	10	7	17
Paternal syphilis, not neurosyphilis	8♂ 6♀		
Paternal dementia paralytica	2♂ 1♀		
	10♂ 7♀		
Congenital syphilis in brothers and/or sisters, paternal syphilis absent or unknown	24	13	37
No data except congenital syphilis in brothers and/or sisters	22♂ 12♀		
Mental disease in nonsyphilitic member of family	2♂ 1♀		
	24♂ 13♀		
Total number of cases with congenital syphilis in brothers and/or sisters	49	38	87

fact that the mother of every congenitally syphilitic child is herself syphilitic. It must be assumed in these 54 cases that the mother either was not examined or did not present clinical or serologic evidence of syphilis at the time of the examination.

Because the error resulting from the failure to report the status of siblings is great it seems inadvisable to draw any definite conclusions from the figures in table 6.

#### INCIDENCE OF NEUROSYPHILIS IN THE FAMILY

Of special interest in this study is the incidence of neurosyphilis in other members of the family.

Of the 399 cases (of the total series of 653 cases) in which definite information about the family history was obtained, in 143 cases (36.8 per cent) neurosyphilis was present in one or more members of the family. Even if one assumes that there was no neurosyphilis in the family in any of the 254 cases in which no family history was given (which is very improbable) the 143 cases represent 22.5 per cent of the total of 653 cases, a remarkably high incidence of neurosyphilis. This figure is even more significant when one considers that this series does not include cases of asymptomatic neurosyphilis, the patients all showed clinical as well as serologic evidence of neurosyphilis. The percentage of clinical neurosyphilis is about 10 per cent as contrasted to this figure of 22.5 per cent. The figure for dementia paralytica represents less than 5 per cent of the incidence of all the manifestations of late

TABLE 7—Incidence of Neurosyphilis in the Family

Type of Neurosyphilis and Member of Family Involved	Cases in Boys	Cases in Girls	Cases in Which Sex Was Not Stated	Total Number of Cases
Dementia paralytica	49	47		96
In both parents	6♂ 0♀			
In mother	14♂ 10♀			
In father	23♂ 28♀			
In siblings	5♂ 9♀			
In uncle	1♂ 0♀			
	49♂ 47♀			
Neurosyphilis other than dementia paralytica	24	14	9	47
In both parents	3♂ 1♀			
In father	12♂ 1♀ 6			
In mother	9♂ 12♀ 3			
	24♂ 14♀ 9			
Total number of cases with neurosyphilis in family	73	61	9	143

syphilis (Turner<sup>3</sup>) in contrast to 14.7 per cent as observed in this series of parents and brothers and sisters of patients with juvenile dementia paralytica. Tables 8 and 9 indicate the incidence of maternal, paternal and fraternal dementia paralytica and their associations with syphilis and mental disease in the family.

The obvious fact shown in tables 8 and 9 is that juvenile dementia paralytica is not transmitted consistently to a member of the same sex as was suggested by Frölich.<sup>4</sup> In this series 20 sons with juvenile dementia paralytica and only 10 daughters with the disease were born to a total of 30 mothers with dementia paralytica. In the 57 instances of paternal dementia paralytica the offspring were female in 23 and male in 34 cases. The unusual association of dementia paralytica in both

3 Turner, T. B. The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, *Bull. Johns Hopkins Hosp.* 46:159, 1930.

4 Frölich, W. Ueber allgemeine progressive Paralyse der Irren vor Abschluss der körperlichen Entwicklung, *Inaug. Dissert.*, Leipzig, Bruno Georgi, 1901.

the father and the mother is recorded in 6 instances (Major,<sup>5</sup> McDowall,<sup>6</sup> Baudouin and Levy-Valenski,<sup>7</sup> Straussler<sup>8</sup> Lafora<sup>9</sup> and Menninger<sup>10</sup>) My own case has not previously been reported in detail

CASE 7<sup>11</sup>—A white youth, aged 19, was admitted to the institution in which his father and mother had died of dementia paralytica There were no other siblings Though the patient was retarded in learning to walk, until the age of 8 or 9 years he had been regarded as unusually bright and intelligent At the age of 8 he fell from a merry-go-round, striking the back of his head At 10 he

TABLE 8—*Incidence of Dementia Paralytica in the Mother*

Association with Syphilis and Mental Disease in Family	Cases in Boys	Cases in Girls	Total Number of Cases
Dementia paralytica in father	5	0	5
Dementia paralytica in father and congenital syphilis in sibling	1	0	1
Syphilis, not neurosyphilis, in father	4	2	6
Congenital syphilis in siblings	0	2	2
Congenital syphilis in siblings and mental disease in family	1	0	1
Mental disease in nonsyphilitic member of family	2	0	2
No data except dementia paralytica in mother	7	6	13
Total	20	10	30

TABLE 9—*Incidence of Dementia Paralytica in the Father*

Association with Syphilis and Mental Disease in Family	Cases in Boys	Cases in Girls	Total Number of Cases
Dementia paralytica in mother	5	0	5
Dementia paralytica in mother and congenital syphilis in sibling	1	0	1
Syphilis, not neurosyphilis, in mother	4	8	12
Syphilis, not neurosyphilis, in mother and congenital syphilis in sibling	0	2	2
Congenital syphilis in sibling	2	1	3
Mental disease in nonsyphilitic member of family	4	1	5
Dementia paralytica in relative other than mother of sibling	2	0	2
No data except dementia paralytica in father	16	11	27
Total	34	23	57

5 Major General Paralysis in a Boy, Brit M J 2 1339, 1892

6 McDowall, C F F General Paralysis in Father, Mother and Son, J Ment Sc 54 562, 1908

7 Baudouin, A, and Levy-Valenski, J Paralysie generale juvenile chez une malade dont le pere et la mere sont morts de paralysie generale, Encephale 2 490, 1910

8 Straussler, E Ueber Entwicklungsstorungen im Zentralnervensystem bei der juvenilen progressiven Paralyse und die Beziehungen dieser Erkrankung zu den hereditaren Erkrankungen des Zentralnervensystems, Ztschr f d ges Neurol u Psychiat 2 30, 1910

9 Lafora, G R Zur Histopathologie der juvenilen Paralyse mit Mitteilung zweier Falle, Ztschr f d ges Neurol u Psychiat 15 281, 1913

10 Menninger, W C Juvenile Dementia Paralytica Study of Forty Cases J A M A 95 1499 (Nov 15) 1930

11 Cases 1 to 6 have been reported in Menninger, W C Juvenile Dementia Paralytica I Incidence Sex and Age at Onset Am J Syph & Neurol 18 486 (Oct) 1934

began to ramble in his speech, talking in a silly manner, and talipes began to develop. The latter condition grew worse, but the patient did not become incapable of locomotion until the age of 14. His vision became impaired at about 13, and since he was 17 the family had doubted whether he could see. For five years he had been unable to speak intelligibly, and dysphagia had been marked. He was completely helpless on admission. Physically he was markedly emaciated, he showed contractures of the lower limbs and athetoid movements of the fingers. The neurologic findings included fixed, unequal, irregular pupils, a bilateral Babinski sign, exaggerated, bilaterally equal deep reflexes and ankle clonus on the left. No stigmas were present. Laboratory data were not available.

The patient could take only a liquid diet and vomited occasionally. Rhythmic jerky movements of the head developed. He died three months after admission, the duration of the disease was approximately ten years.

There are references to some other cases in which the mother and father had dementia paralytica, though none can be verified. One author, Amelien, has been rather widely cited as reporting 6 such cases, but no references are given. A French worker, Ameline,<sup>12</sup> in 1900 did report

TABLE 10—*Incidence of Dementia Paralytica in Brothers and Sisters*

	Total Number of Males	Total Number of Females	Total Number of Cases
Dementia paralytica			
In other brothers or sisters alone	0	8	8
With syphilis, not neurosyphilis, in father	0	3	3
With syphilis, not neurosyphilis, in mother	4	1	5
With mental disease in the family	1	0	1
Total number of cases in which brothers or sisters had dementia paralytica	5	12	17

6 instances in which dementia paralytica occurred in a parent and an offspring, in 4 instances in the father and son, in 2, in the mother and daughter, and in 1, in a maternal uncle and a nephew. However, none of his cases were presumed to be definite instances of congenital syphilis, and he did not give sufficient evidence to decide the point.

The incidence of dementia paralytica in the brothers or sisters is indicated in table 10.

There are, according to this table, 17 instances in which some other sibling in the family had juvenile dementia paralytica. There are reports of 2 cases in which three members of the same family were affected—that of Homen,<sup>13</sup> who cited the case of three girls aged 12, 20 and 21 and that of Kingery,<sup>14</sup> whose patients were aged 2, 4 and 7 years. Cases similar to those of Kingery recently came under my observation.

12 Ameline. De l'hérédité et en particulier de l'hérédité similaire dans la paralysie générale, *Ann med-psychol* **11** 459, 1900.

13 Homen, E. A. Eine eigenthümliche Familienkrankheit, unter der Form einer progressiven Dementia, mit besonderem anatomischen Befund, *Neurol Centralbl* **9** 514, 1890.

14 Kingery, L. B. A Study of the Spinal Fluid in Fifty-Two Cases of Congenital Syphilis, *J A M A* **76** 12 (Jan 1) 1921.

Three boys, aged 7, 5 and 3, had parents who showed no clinical evidence of syphilis and had negative Wassermann tests of the blood, though both had received antisyphilitic treatment. The paternal grandmother had been treated for syphilis. The boy aged  $7\frac{1}{4}$  years was sickly as a baby, ate poorly and was said to have rickets. He never walked alone and acquired a vocabulary of about fifty words. In his third year he began sitting around doing nothing, and it was noted that his pupils were unequal. He was treated for "thyroid trouble." Convulsions began in the fourth year, and in the fifth the spinal fluid was found to have a positive Wassermann reaction. On examination he showed marked hydrocephalus, pes cavus, advanced chorioiditis, bilateral optic atrophy, fixed unequal pupils, apparent deafness, a bilateral Babinski sign and Hutchinson's teeth. The Wassermann reaction of the blood was positive, but the spinal fluid could not be examined. The second child, a boy aged  $5\frac{1}{4}$  years, appeared to be in good health till 4 months of age when "stomach trouble" developed. He walked at 13 months, talked at 15 months and seemed to develop normally. At the age of 5 years he became sulky, refused to obey and was irritable, abusive and much less talkative than formerly. He presented unequal, nearly fixed pupils, used a pronounced baby talk and showed an inability to respond to the simplest commands, hyperactive deep reflexes and a positive Wassermann reaction of the blood. The third child, a boy aged  $3\frac{1}{3}$  years, sat up at 6 months and walked at 17 months, but his legs seemed weak and he resorted chiefly to crawling. He developed physically and seemed well until 3 years of age, when an infection of the scrotum developed from a splinter. Following this, an ankle and then one knee became swollen. He presented pupils nearly fixed to light, hyperactive deep reflexes and a tremendous hydrocephalus.

Other reports of two children with juvenile dementia paralytica in the same family were given by Hoch,<sup>15</sup> Jouschenko (1896), von Speyr (1899, the mother was tabetic), Sollier (1910), Triapet (1910), Huguet (1913), Kron (1915), Muller-Hess (1919, the mother had tabes), Grutter (1920), Long-Landry (1921, the father was tabetic) and two other children had neurosyphilis), Klauder and Solomon,<sup>16</sup> Potter<sup>15</sup> and myself<sup>10</sup>

*Familial Predisposition to Neurosyphilis in Three Generations*—While the occurrence of syphilis in the third generation seems fairly well established,<sup>17</sup> it is extremely rare and difficult to prove beyond question. There are, however, several reported cases in which neurosyphilis appeared in three successive generations, this may certainly indicate a familial predisposition to neurosyphilis, even when the direct transmission is doubtful. In the aforementioned family of three boys with congenital neurosyphilis, the paternal grandmother had syphilis beyond doubt, and from the description given it was likely neurosyphilis, though

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15 To avoid duplication, a bibliography listing all individual reports of cases will be given at the conclusion of a subsequent study.

16 Klauder, J. V., and Solomon, H. C. Juvenile Paresis, with Presentation of Twenty-Three Cases, *Am J M Sc* **166** 545 (Oct.) 1923.

17 Sams, W. M. Third Generation Syphilis, *Am J Syph & Neurol* **17** 492, 1933.



no examination was possible. The following case also indicates the presence of probable neurosyphilis in three generations.

CASE 8—A girl was aged 14 on admission. At least three grandparents were treated for syphilis, and one grandfather died at 54 of tabes. The father, mother and one brother all attended the clinic for syphilitic patients at the Bellevue Hospital and had positive Wassermann tests of the blood. Another brother, aged 16, was mentally defective. The patient had a normal birth and developed normally until vision began to fail at 9 years and was completely gone at 10 years. She had always been a bright child, of happy disposition, she had many friends, liked to study and was quiet and obedient. She was fond of music and played the piano well for her age. At 13 years of age she became nervous, and twitchings of the right arm developed. She became irritable and sleepless and stopped attending school at 14 because of nervousness. She became resistive and at times excited and stubborn. Ten days before admission she became disturbed, laughed and cried alternately, rolled on the floor and tore off her clothes. Physically she was well developed and well nourished. Neurologically she showed optic atrophy, fixed pupils, coarse nystagmus, defects of speech, incontinence and an absence of the knee jerk on the left. She had an ataxic gait. Stigmas were not present. Mentally she was alternately mute and noisy, restless and depressed. She was resistive, negativistic and gave no cooperation, and restraint was occasionally necessary. Laboratory examination showed positive Wassermann tests of the blood and spinal fluid, increased globulin, no cells and a colloidal gold curve of 4554332110.

She had received two months' treatment with arsphenamine before admission. She was given tryparsamide regularly for the following eleven months, malaria therapy was regarded as inadvisable because of her general condition. She showed slight improvement, but she remained silly and no change occurred in the physical signs. Her parents thought that she was better and paroled her eleven months after admission.

In 1910, Lwoff and Condomine<sup>18</sup> reported a case of juvenile dementia paralytica in a girl, aged 20, whose maternal grandmother and mother had dementia paralytica, two aunts and an uncle suffered from mental disease, a cousin was feeble-minded, and four other siblings were mentally deficient, one of these committed suicide. Leavitt<sup>19</sup> reported a case of juvenile dementia paralytica in a boy whose maternal grandmother had tabes, the mother had syphilitic disease of the optic nerve and a positive Wassermann test of the spinal fluid. Klauder and Solomon<sup>16</sup> quoted Rieger (reference not given or located) as reporting a family in which the father, son, daughter and granddaughter all had dementia paralytica.

*Neurotropic Strain of Spirochaeta Pallida*—The fact that in 36.8 per cent of the cases in which the family history is known there was evidence of neurosyphilis in some other member of the family is strong

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18 Lwoff and Condomine, A. Un cas de paralysie generale juvenile, *Informateur d alien et d neurol* 5 39 1910

19 Leavitt, F. H. Juvenile Dementia Paralytica Occurring in the Third Generation of a Syphilitic Family, *Arch Neurol & Psychiat* 26 665 (Sept) 1931

clinical evidence toward the theory of the existence of a neurotropic strain of *S. pallida*. However, it is only clinical evidence and not conclusive proof of the existence of such a strain.

Clinical evidence of the existence of syphilis à virus nerveux has been extensive, too much so to be reviewed here. Marie<sup>20</sup> reviewed the subject of a neurotropic strain in cases of hereditary syphilis of the nervous system and gave a hundred references. The studies of Junius and Arndt,<sup>21</sup> von Rohden,<sup>22</sup> Plaut and Goering,<sup>23</sup> Semper,<sup>24</sup> Wahl<sup>25</sup> and Bonneau<sup>26</sup> on the occurrence of neurosyphilis in the descendants of parents with dementia paralytica have been strongly suggestive of the existence of such a strain of spirochetes. And the studies on conjugal neurosyphilis of Junius and Arndt,<sup>21</sup> Schacherl,<sup>27</sup> Raven,<sup>28</sup> Seelert<sup>29</sup> and Moore and Kemp<sup>30</sup> have also supported such a hypothesis. Kemp and Poole's<sup>31</sup> study of the incidence of neurosyphilis among the parents of congenitally syphilitic children is especially suggestive. In a group of 20 families with congenitally neurosyphilitic children and in a group of 20 families with congenitally syphilitic children without neurosyphilis, they found that neurosyphilis was eight times as frequent among the mothers and over three times as frequent among the fathers in the neurosyphilitic group. They pointed out, however, that familial predisposition to neurosyphilis may be just as much a factor as a possible neurotropic strain.

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20 Marie, A. Heredo-syphilis et paralysie generale infantile, Bull. Soc. franç. de dermat. et syph. **33** 153 (March) 1926.

21 Junius, P., and Arndt, M. Ueber die Deszendenz der Paralytiker, Ztschr. f. d. ges. Neurol. u. Psychiat. **17** 303, 1913.

22 von Rohden, F. Ueber die Pathologie der Paralytikerfamilie, Ztschr. f. d. ges. Neurol. u. Psychiat. **37** 110, 1917.

23 Plaut, F., and Goering, M. H. Untersuchungen an Kindern und Ehegatten von Paralytikern, Munchen med. Wchnschr. **58** 1959, 1911.

24 Semper. Les enfants des paralytiques generaux, These de Paris, 1904.

25 Wahl. Contribution a l'etude de la descendance des paralytiques generaux, These de Paris, 1898.

26 Bonneau. L'héredite simalaire dans la paralysie generale, Thèse de Paris, 1909.

27 Schacherl, M. Ueber Luetikerfamilien, Jahrb. f. Psychiat. u. Neurol. **36** 521, 1914.

28 Raven, W. Serologische und klinische Untersuchungen bei Syphilitiker-Familien, Deutsche Ztschr. f. Nervenhe. **51** 342, 1914.

29 Seelert, H. Untersuchungen der Familienangehörigen von Paralytikern und Tabikern auf Syphilis, Monatschr. f. Psychiat. u. Neurol. **41** 329, 1917.

30 Moore, J. E., and Kemp, J. E. Studies in Familial Neurosyphilis. III. Conjugal Neurosyphilis, Arch. Int. Med. **32** 464 (Sept.) 1923.

31 Kemp, J. E., and Poole, A. K. Familial Neurosyphilis. IV. Incidence of Neurosyphilis Among the Parents of Congenitally Neurosyphilitic Children, J. A. M. A. **84** 1395 (May 9) 1925.

There is, however, clinical evidence against such a theory. There are numerous recorded instances of neurosyphilis affecting several members of a family, each acquiring syphilis from a different source (Moore and Keidel<sup>32</sup>), as Stewart<sup>33</sup> pointed out. Furthermore, it is rather common to find patients with juvenile dementia paralytica without stigmas or cutaneous or osseous syphilis whose brothers or sisters show pronounced stigmas or cutaneous or osseous syphilis. Dennie<sup>34</sup> expressed the belief that there is only slight clinical evidence of transmission of dementia paralytica from parents to their offspring, the malady may develop in the first child, and the others may escape without any clinical form of neurosyphilis.

Moore<sup>35</sup> has summarized the experimental evidence by stating that the problem is not proved. He reviewed the unconfirmed work of Reasoner<sup>36</sup> with a strain of spirochetes particularly prone to produce chorioretinitis in rabbits. Levaditi and Marie's<sup>37</sup> work on differentiation of neurotropic and dermatropic strains has been especially questioned by Jahnel,<sup>38</sup> who believed that they confused their neurotropic strain with *Treponema cuniculi*, the organism of spontaneous spirochetosis in rabbits. The unconfirmed work of Plaut and Mulzer<sup>39</sup> with a strain which causes a high proportion of rabbits to show pleocytosis in the spinal fluid was uncontrolled with regard to the confusing factor of spontaneous encephalitis in rabbits.

Consequently, the hypothesis of the existence of a neurotropic strain must still be left in the balance, despite clinical evidence. Certainly the clinical evidence mustered could be equally applied to the theory of a familial predisposition to neurosyphilis. And furthermore it is likely

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32 Moore, J. E., and Keidel, A. Studies in Familial Neurosyphilis. II. Familial Neurosyphilis from Various Extra-Marital Sources. A Clinical Contribution to the Question of Neurotropism, *J. A. M. A.* **80** 1818 (March 24) 1923.

33 Stewart, R. M. Juvenile Types of General Paralysis, *J. Ment. Sc.* **79** 602 (Oct.) 1933.

34 Dennie, C. C. Familial Neurosyphilis, *J. A. M. A.* **95** 1571 (Nov. 22) 1930.

35 Moore, J. E. The Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 36.

36 Reasoner, M. A. Some Phases of Experimental Syphilis with Special Reference to the Question of Strains, *J. A. M. A.* **67** 1799 (Dec. 16) 1916.

37 Levaditi, C., and Marie, A. Etudes sur le treponeme de la paralysie générale, *Ann. Inst. Pasteur* **33** 741, 1919.

38 Jahnel, F. Das Problem der progressiven Paralyse, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **76** 166, 1922.

39 Plaut, F., and Mulzer, P. Die Liquordiagnostik im Dienste der experimentellen Kaninchensyphilis. München med. Wchnschr. **69** 496, 1922.

that there are determining factors, as yet undefined and possibly unsuspected, inherent in the subject which may be far more important than the strain or virulence of the infecting organisms

#### INCIDENCE OF MENTAL DISEASE IN THE FAMILY

Exclusive of dementia paralytica, mental disease sufficiently severe to necessitate hospitalization occurred in 55 instances in the 399 cases in which the history is known. This figure represents not the entire number of mentally ill relatives but rather the number of cases of

TABLE 11—*Incidence of Mental Disease in the Family*

Association with Syphilis		Cases in Boys	Cases in Girls	Total Number of Cases
Both parents syphilitic		4	0	4
Both parents with syphilis, not neurosyphilis	2♂ 0♀			
Congenital syphilis in siblings	1♂ 0♀			
Paternal dementia paralytica and maternal syphilis, not neurosyphilis	1♂ 0♀			
	4♂ 0♀			
Maternal syphilis		4	4	8
Maternal syphilis, not neurosyphilis	3♂ 1♀			
Congenital syphilis in siblings	0♂ 1♀			
Maternal dementia paralytica	1♂ 2♀			
	4♂ 4♀			
Paternal syphilis		6	2	8
Paternal syphilis, not neurosyphilis	2♂ 1♀			
Paternal dementia paralytica	4♂ 1♀			
	6♂ 2♀			
Congenital syphilis in siblings (paternal and maternal syphilis absent or unknown)		3	1	4
Dementia paralytica in relative (uncle) and no other data		1	0	1
No data on syphilis in any member of family		18	12	30
Total number of cases with mental disease in immediate family		36	19	55

juvenile dementia paralytica in which mental disease occurred in some member of the family. In most instances the incidence of mental disease was a matter of historical data and not subject to verification on the part of the examiner. Consequently it is not possible to state whether or not some of the reported cases of mental illness were instances of syphilis. In most reports it was merely stated that the persons were "insane."

These 55 cases represent 13.7 per cent of the 399 cases in which the family history was given and 8.4 per cent of the total of 653 cases. These figures are both very high as contrasted to the incidence of mental disease (as indicated by the number of resident patients in state hospitals) in the average population, which is roughly about 0.004 per cent (about 400 in each 100,000 of population).

The incidence of mental disease in the family in these cases and its association with syphilis in other members of the family are shown in table 11. The significance of this high incidence of mental disease in the families of patients with juvenile dementia paralytica cannot be stated. It may support the theory of *erbliche Belastung* as applied to dementia paralytica by Naecke,<sup>40</sup> Raymond<sup>41</sup> and Schule<sup>42</sup> and to juvenile dementia paralytica by Alzheimer<sup>43</sup> and Coquerelle<sup>44</sup>. On the other hand, Schmidt-Kraepelin<sup>45</sup> could find no evidence in her cases that this "burdening with hereditary traits" is of any significance in the development of juvenile dementia paralytica. She believed that it is no more pronounced than in the cases of adults with dementia paralytica, while Kalb (quoted by Schmidt-Kraepelin), on the basis of exhaustive studies, stated that there existed no influence of special hereditary impairments. On the other hand, Ameline<sup>12</sup> believed that heredity played a part in the transmission of adult dementia paralytica and found 7 cases in a series of 238 in which following dementia paralytica in the first generation the malady developed in a member of the second generation (and the syphilis was probably not congenital).

In regard to the influence of heredity it seems incorrect to compare the juvenile type and the acquired type of dementia paralytica. In the congenital cases one must consider the damaging effect of syphilis on the germ plasma (the parasymphylis of Fournier) together with the family inheritance, while in the acquired form only the family inheritance plays a part. The high incidence of mental disease in the family in this large series of cases of juvenile dementia paralytica certainly suggests the existence of a predisposition to vulnerability of the central nervous system.

#### SUMMARY AND CONCLUSIONS

1 In the entire series of 653 cases of juvenile dementia paralytica the presence of syphilis clinically or serologically (or both) was established in one or more members of the family in 369 instances (56.5 per cent).

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40 Naecke, P. Der endogene Faktor in der Pathogenese der Paralyse, *Ztschr f d ges Neurol u Psychiat* **18** 280, 1913.

41 Raymond, F. *Etudes de pathologie nerveuse. Maladies familiales*, Paris, H. Delavue, 1910.

42 Schule, H. Statistische Ergebnisse aus 100 Fallen von progressiver Paralyse, *Jahrb f Psychiat u Neurol* **22** 18, 1902.

43 Alzheimer. Die Fruhform der allgemeinen progressiven Paralyse, *Allg Ztschr f Psychiat* **52** 533, 1895.

44 Coquerelle, A. Contribution à l'étude des rapports de la paralysie generale juvénile et de l'heredosyphilis, Thèse de Paris, 1922.

45 Schmidt-Kraepelin, T. Ueber die juvenile Paralyse, Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, no 20, Berlin, Julius Springer, 1920.

2 While maternal syphilis is known to be present in every instance in which there is a congenitally syphilitic offspring, it was demonstrated as present in 223 cases. Syphilis was manifest as neurosyphilis in 26 per cent of the 223 cases of maternal syphilis, as compared to 6.4 per cent, the incidence of clinical neurosyphilis in women (in the clinic of the Johns Hopkins Hospital). Thus mothers of patients with juvenile dementia paralytica show nearly four times the frequency of clinical neurosyphilis exhibited in average groups of syphilitic women.

3 Maternal neurosyphilis in cases of juvenile dementia paralytica is about equally distributed between dementia paralytica and other clinical types of neurosyphilis.

4 Paternal syphilis was demonstrated in 226 cases, of which 35.4 per cent were cases of neurosyphilis. The average incidence of clinical neurosyphilis in males is 20.38 per cent (clinic of the Johns Hopkins Hospital), which indicates that the fathers of patients with juvenile dementia paralytica show nearly twice the incidence of clinical neurosyphilis present in average groups of syphilitic men.

5 Dementia paralytica in the father occurred twice as frequently as all other forms of neurosyphilis (57 with dementia paralytica and 23 with other types) and in these cases the patient was male in 49 cases and female in 25 cases. These findings suggest the predisposition for paternal transmission of dementia paralytica.

6 Both parents were demonstrated to have syphilis in 72 cases (11 per cent), and in these 72 cases neurosyphilis was present in one or both parents in 29 instances (40.3 per cent).

7 Neurosyphilis was demonstrated in some member of the family (other than the patient) in 143 instances, or 22.5 per cent of the 653 cases surveyed, a figure nearly twice as large as that for the average incidence of clinical neurosyphilis. Dementia paralytica occurred in 14.7 per cent of the cases, which is three times the average incidence of that disease.

8 Dementia paralytica was present in the mothers of 20 males and of 10 female patients with juvenile dementia paralytica. It was present in the fathers of 34 male and of 23 female patients. It was present in both parents in 6 instances, the patient being male in each case. Such findings do not substantiate the transmission of dementia paralytica through the same sex.

9 Dementia paralytica was present in a brother or sister of the patient in 17 instances.

10 Several instances of neurosyphilis in three generations of a family are cited, furnishing further clinical evidence for familial predisposition to neurosyphilis.

11 The high incidence of neurosyphilis (36·8 per cent), the high percentage of dementia paralytica in the parents (14·7 per cent), the numerous instances of two or more siblings with neurosyphilis and the presence of neurosyphilis in three generations all lend clinical support to the theory of a neurotropic strain of *S. pallida* but might equally well support the theory of a familial predisposition to neurosyphilis.

12 Mental disease occurred in one or more nonsyphilitic members of the family in 55 instances. This high incidence of mental disease supports the theory of *erbliche Belastung* of the earlier German writers as well as of many others that juvenile dementia paralytica occurs frequently in a "degenerate" family stock.

# TOXEMIA OF PREGNANCY

ITS RELATION TO CARDIOVASCULAR AND RENAL DISEASE,  
CLINICAL AND NECROPSY OBSERVATIONS WITH A  
LONG FOLLOW-UP

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This article on toxemia of pregnancy is based on the study of this condition at the Sloane Hospital for Women during the past fifteen years. Nine hundred and thirty cases have been observed, 594 of which have been followed up in at least semiannual examination by the medical rather than by the obstetric attending staff. The object of the study has been to find out what type of woman is subject to the condition during pregnancy and what pathologic changes are present not only at the time of the toxemia but in the years following. Of importance also are the life expectancy of these patients, the cause of death and the observations at necropsy.

Our observations suggested that the toxemias may not be isolated, idiopathic states but that they are possibly related to certain common general medical conditions. That this suspicion may have some foundation is suggested by important statistical figures. Of the 594 women followed up for an average period of five and six-tenths years, with extremes of one year and twenty-two years, 90, or 15.7 per cent, have died. This figure becomes 2.7 per cent if calculated on the basis of the death rate in the general female population between the ages of 20 and 45 years, which is 0.4 per cent. In other words, the mortality rate in the group studied is almost seven times the average death rate for women of child-bearing age. Of the 90 deaths, 72, or 80 per cent, were from causes within the cardiovascularrenal field. This observation fits in with impressions gained from the clinical follow-up studies, namely, that the victim of toxemia of pregnancy is peculiarly liable to such serious sequelae as nephritis and hypertensive cardiovascular disease. This was pointed out by Corwin and one of us (W. W. Herrick), who before the Association of American Physicians in 1927 reported a clinical study of 239 cases in which nephritis was present in 64, or 26.7 per cent, and hypertensive cardiovascular disease in 175, or 73.2 per cent, of the patients followed up from six months to six years after the toxemia.

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One of the chief difficulties in the follow-up study of patients with these conditions, and perhaps the dominant occasion for this report, is the lack of logical classification of the toxemias and particularly of their sequelae. In most obstetric clinics a woman with high blood pressure is classified as having nephritis. Primary vascular disease with hypertension is still unrecognized. The differential diagnosis of primary nephritis and primary hypertensive cardiovascular disease need not be discussed here. It is true that the clinical differentiation is not always possible, especially in the end-stages. A pathologist, however, differentiates with more assurance.

From our studies we are convinced that the thread of one of these two conditions runs through at least a majority of the instances of toxemia. We believe that it is generally possible and highly important to separate these threads during gestation and in the follow-up period because of the difference in prognosis for both the mother and the child and the difference in suitable management of the mother.

The contrasting clinical pictures of the toxemias related to primary nephritis and those related to hypertensive cardiovascular disease may be set forth best by describing what happens when pregnancy takes place in a woman already afflicted with either malady.

In the case of established nephritis, whether latent or manifest, pregnancy activates and aggravates roughly in proportion to the size of the fetus. In other words, serious manifestations usually occur late in the period of gestation. The dominant sign of nephritis is albuminuria. In nephritis complicating pregnancy this is marked and persistent. Hypertension may or may not be present, but often appears after the onset of albuminuria or not until the later phases of the disease. There is a tendency to retention of nitrogen, to an albuminuric type of retinitis, to anemia and to edema, to early death of the fetus in about 60 per cent of the cases, and in more serious instances to uremia, occasionally with convulsions. With death of the fetus or with delivery the symptoms may or may not clear away promptly. In the follow-up period, however, the majority of patients reveal persistent albuminuria and often hypertension, retinitis and other evidences of nephritis. The life expectancy is relatively short, and death from uremia or infection is the rule. Should reproduction again be attempted, the renal breakdown appears earlier in pregnancy and is usually more serious, and the result is less likely to be a living child. In a woman with nephritis, repeated pregnancy seems to encroach further on the factor of safety of the kidney and should be avoided.

If pregnancy takes place in a woman who is subject to hypertensive cardiovascular disease, however mild, a quite different series of events may be expected in the average case. As gestation advances the diastolic as well as the systolic blood pressure tends to rise. Usually no distur-

bance other than the hypertension is noted either by the physician or by the patient until the blood pressure reaches 180 systolic and from 110 to 120 diastolic. Rather abruptly at this point a slight or pronounced albuminuria, often of varied amount, may appear. If the condition progresses, a decline in the renal output, and edema, may follow. To this may be added evidence of hepatic degeneration in epigastric pain and tenderness, perhaps with icterus. Changes in mentality may be noted, exaggerated deep reflexes may appear and typical eclampsia with convulsions may take place. The retinal picture is important. The arteries at first are small and spastic and may constrict the veins. Hemorrhages may occur. In case of eclampsia diffuse edema is often added, and retinal separation with a fairly good prognosis as to vision may be seen. Patches of white exudate are not frequently seen. In contrast to the nephritic group, there is no retention of urea nitrogen in the blood. The uric acid content of the blood may be increased.

This process may be rapid in its development, as in acute eclampsia, or may be slow, extending over a period of many weeks, it may be arrested at any stage, some of the milder cases showing only a moderate rise in blood pressure with or without slight and variable albuminuria.

In the cases of eclampsia in our series (70) the immediate maternal mortality was 17.1 per cent, during the follow-up period 22.5 per cent of the survivors died. The immediate fetal mortality was 60.9 per cent. In the milder, nonconvulsive cases the maternal deaths were few and the fetal mortality was not over 15 per cent. If albuminuria and edema can be controlled, cases with moderate hypertension, especially those in which it appears late in pregnancy, can usually be carried on to viability of the fetus or to term.

The behavior of this type of patient in future pregnancies is variable. Eclampsia recurred in 14.3 per cent of the 70 patients, but an appreciable percentage of women with eclampsia in later pregnancies present a mild disturbance marked by hypertension. For example, Corwin and Herrick cited a consecutive series of 154 multiparas with toxemia 13 per cent of whom gave a history of convulsions in previous pregnancies. In the patients of this group without a history of convulsions the same observers found a recurrence of hypertension in 96 per cent showing a tendency to higher ranges in later pregnancies in the majority.

The clinical follow-up study of the patients with toxemia marked by hypertension as the dominant feature with albuminuria secondary and subsidiary appeared to reveal the stigmas of hypertensive cardiovascular disease rather than those of primary nephritis, that is, in patients who had enduring sequelae of toxemia. At the end of the first year of follow-up about 30 per cent revealed a blood pressure above 150. After the third year this state was observed in over 50 per cent. More than 50 per cent revealed some degree of sclerotic change

in the retinal arteries Albuminuria was variable but was present in some amount, however small, in about 20 per cent Cardiac enlargement and thickening of the larger palpable arteries were common Edema was rare Most of the women in the group were large of frame and obese and were more inclined to plethora than to anemia We classified the patients showing sequelae of this kind in the follow-up period in the group with hypertensive cardiovascular disease rather than in that with primary nephritis In the group with cardiovascular disease the common causes of death were cardiac failure and apoplexy In a few instances uremia dominated the final picture, presumably the consequence of renal arteriosclerosis

While the clinical evidence of the existence of these two types of disturbance in association with or following toxic pregnancy is suggestive the evidence from the necropsies seems almost conclusive Thus far in our series of cases with a long follow-up period 11 necropsies have been performed by competent pathologists These examinations have been made without the knowledge on the part of the pathologist that any special interest was attached to the subjects One examination was made in the hospital of the Rockefeller Institute and the rest in the Presbyterian Hospital The necropsy observations corroborated the clinical observations Two distinct types of cases were described by the pathologist In 4 cases the postmortem diagnosis of primary glomerulonephritis was made, and in 7, that of primary cardiovascular disease with arteriolosclerosis

The kidney of the patient with acute eclampsia has frequently been described It presents a degenerative process showing profound changes in the glomeruli and in the contributory and component vessels with lesser alterations in the tubules Fahr spoke of this as glomerulonephrosis Signs of inflammation are absent The glomeruli are swollen and devoid of blood and exhibit fatty degeneration There are significant widening and swelling of the walls of the glomerular capillaries and of the afferent arterioles with subsequent hyalinization and secondary tubular atrophy The process in the glomeruli seems to be one of ischemic necrosis which is the result of narrowing of the vascular channels by swelling of the walls or by spasm The theory of ischemic necrosis caused by spasm receives some support from the study of the capillaries of the nail fold in cases of eclampsia and particularly from the study of the retina Spasticity of the retinal arteries is an early feature of the vascular type of toxemia of pregnancy This is often followed by edema and other forms of retinal degeneration and rarely by separation, in many instances a later development is definite arteriosclerosis

Few pathologists have studied the eclamptic kidney after a long follow-up period Bell has described the case of a patient on whom

necropsy was performed seven years after the eclampsia. Although Bell considered that capillary thickening and the hyalinization of the glomeruli were evidence of a peculiar kind of disease of the kidney, he stated that "the findings, including cardiac hypertrophy, suggest that the patient must have had hypertension."

The changes in the renal structure found by Bell seem to differ in no essential particular from those in our 3 cases of eclampsia with more detailed clinical study. The changes were considered by members of the department of pathology of the Presbyterian Hospital to be characteristic of the end-stage of cardiovascular disease with hypertension. In 1 case the renal lesions were very slight, the principal changes being in the arteries of the spleen, pancreas, suprarenal glands and liver. It is of no small significance that in the remaining 4 of the 7 cases, which were examples of nonconvulsive and milder types of vascular toxemia and which we considered to be nonnephritic, verifying observations were made both in the clinical follow-up and at autopsy. This is further evidence of a fact that has been shown repeatedly that the necropsy observations in cases of nonconvulsive, preeclamptic and milder types of toxemia are identical with those in cases of eclampsia.

The clinical and pathologic evidence suggests a continuous chain of events in cases of toxemia with cardiovascular sequelae. The vascular damage of the acute phase of the disease may not be repaired but may become permanent, leading in at least half the cases to the manifestations of hypertension in the follow-up period and to ultimate disclosure at autopsy of characteristics of this generalized disease of the arterial system which ends in cardiac failure, apoplexy or renal failure through narrowing of the vascular channels supplying the kidneys.

#### SUMMARY

A group of 594 cases of toxemia of pregnancy has been studied by internists during the period of toxic gestation and during a follow-up period averaging five and six-tenths years, with extremes of one and twenty-two years. The death rate in this group was 27 per cent, based on the mortality figures for women in general between the ages of 20 and 45 years in the city of New York, which is 0.4 per cent. The mortality in this group, without reference to the comparative death rate in the average female population, was 15.7 per cent. Of the deaths among 594 cases followed up, 80 per cent were from causes within the cardiovascular-renal field.

From a medical point of view the cases fall into two groups. The first, and smaller, is associated with a latent or manifest primary glomerulonephritis and the second, and larger, with hypertensive cardiovascular disease. These differ in their clinical manifestations during the toxemia and in the follow-up period and also in the prognosis and

treatment More than one-half the survivors of toxic pregnancy reveal symptoms and signs of one or the other of these conditions within three years

Among the 594 cases 11 have come to necropsy In these the pathologists, independently of the clinic, have described two types of disease In 4 cases there were changes typical of chronic glomerulonephritis, and in 7, changes characteristic of cardiovascular disease with hypertension

It seems probable that the pathologic changes characteristic of eclampsia, preeclampsia and other vascular types of toxemia are not transitory but in over 50 per cent of the cases are permanent, merging into those of chronic vascular disease as disclosed in this group at necropsy

#### REPORT OF CASES AND NECROPSY OBSERVATIONS

The hypertensive group comprises 7 cases

**CASE 1—History**—E L, aged 28, an American, was a multipara The personal and family history gave no evidence of cardiovascular disease or of infection The patient was in good health until six years before death, when the first pregnancy occurred The blood pressure and urine were normal at the third month, but in the seventh month there was edema with high blood pressure and convulsions Cesarean section was performed, with death of the infant The patient was well for the next four years, but the blood pressure remained high and albuminuria persisted Two years before the final admission to the hospital the patient became pregnant, and a therapeutic abortion was done because of edema and vomiting One year later retinal hemorrhage was observed, and shortly afterward the following observations were made blood pressure, 260 systolic and 150 diastolic, albuminuria, retinitis, arteriosclerosis, cardiac hypertrophy, urinous breath, output of phenolsulphonphthalein, 19 per cent, and blood urea, 0.92 mg per hundred cubic centimeters The patient did fairly well until just before the final admission, when edema, insomnia, headache and dyspnea increased She appeared to be chronically ill The retina revealed papilledema, evidence of recent and old hemorrhages, patches of exudate and marked tortuosity of the retinal arteries The heart was enlarged and showed gallop rhythm with an apical systolic murmur Hydrothorax and considerable pulmonary moisture were present The liver was enlarged, and there was well marked edema of the legs The preliminary diagnosis was advanced cardiovascular disease following toxemia of pregnancy six years before

**Laboratory Examination**—There was marked secondary anemia, with an increased blood urea content, which reached a maximum of 1.79 Gm per liter The urine showed a high trace of albumin with a few granular casts The specific gravity was never above 1.012, and the output of phenolsulphonphthalein was 10 per cent after two hours

**Course**—Bilateral hydrothorax increased, the progress continued steadily downward, and the patient died on Oct 13, 1932, with a picture of circulatory failure with pulmonary edema The clinical diagnosis was chronic glomerular nephritis, chronic uremia, cardiac hypertrophy and insufficiency, bilateral hydrothorax, advanced albuminuric retinitis, and hypertension

*Gross Observations at Necropsy*—There was moderate edema of the ankles, and large amounts of fluid were present in the peritoneal cavity and in both thoracic cavities. The heart weighed 500 Gm. The endocardium showed superficial hemorrhages. There was some edema of the leaflets of the mitral valve and hemorrhage was observed in the anterior papillary muscle. Plaques around the openings of both coronary arteries somewhat occluded that of the left artery. The myocardium of the left ventricle was enormously thickened, and that of the right moderately so. There was no fibrosis. Except for a few plaques, which did not cause occlusion, the coronary arteries were normal. The aorta showed a few atheromatous patches. The lungs were edematous. The spleen, liver, pancreas and suprarenal glands were normal. The brain showed moderate subpial edema. The walls of the basal vessels showed no thickening but some yellow atheromatous patches.

*Kidneys*—The kidneys weighed 60 Gm. each and were practically identical. The capsules stripped fairly easily, leaving a granular surface consisting of grayish-red nodules from 1 to 1.5 mm. in diameter, with brownish-red tissue between. The cortex measured from 2 to 4 mm. in thickness. The normal striations were not very distinct. In the cortex no glomeruli could be made out. The renal vessels were prominent.

*Microscopic Observations at Necropsy*—The muscle fibers of the heart were hypertrophied. The intima of the aorta was thickened in several places by increased connective tissue, usually hyalinized close to the muscularis. There was some infiltration by round cells with small hemorrhages, and small scars were present about the nutrient vessels. These areas displayed broken and frayed elastic fibers, some of the arterioles showed thickened walls and some were completely occluded. The walls of the smaller vessels of the spleen and pancreas were thickened and hyalinized almost to complete occlusion of the lumen, and the larger vessels showed plaques of intimal thickening. There were similar, though less marked, changes in the suprarenal arteries. The pituitary gland was normal.

*Kidneys* Under the low power lens the section appeared to be a succession of dilated tubules separated by new and old scars, with little normal renal tissue. Some of the glomeruli were completely hyalinized, but most of them were large, and instead of the normal delicate papillary tufts they contained a mass of cells enmeshed in more or less hyaline material which was often adherent to the edge of the capsule. The capsule in several of the glomeruli was enormously thickened. No crescents were seen. Many of the convoluted tubules were widely dilated, and their cells were desquamated. The terminal tubules were filled with granular casts and were often completely desquamated. A few of them contained polymorphonuclear cells with pinkish coagulum. The interstitial tissue was infiltrated by round cells. The connective tissue was greatly increased, and in it were found areas of atrophied tubules. The smaller branches of the arterioles had thick walls which occasionally were hyalinized, many being completely occluded by their hyalinized walls. Sometimes the vessels entering glomeruli, or even the glomeruli themselves, were occluded by hyaline material. The elastic tissue was reduplicated in certain of the arterioles with a sharp band lacking in elastic tissue. In other arterioles there was a diffuse increase in elastic tissue throughout the thickened wall. In a few arterioles all the elastic tissue appeared to be absent. The elastic tissue in the larger vessels was normal. A considerable number of fine fibers were to be found in the glomerular capsule and in the connective tissue between the tubules.

*Anatomic Diagnosis*—This was generalized arteriosclerosis, advanced arteriolo-nephrosclerosis, myocardial hypertrophy, chronic passive congestion of the lungs and spleen, bilateral hydrothorax, ascites, edema of the extremities, early bilateral lobular pneumonia, encephalomalacia of the left frontal lobe and the cerebellum, and ulcer of the stomach

*Summary*—This was a case of hypertensive disease in a woman under 30 with extreme renal atrophy and characteristic arteriolar changes in the kidneys, the spleen, the suprarenal glands and the aorta. The symptoms were known to date back at least six years to her first pregnancy, which ended in eclampsia

*CASE 2—History*—C. M., aged 45, an Irish multipara, was admitted to the hospital on May 26, 1931, and died on May 30. The last pregnancy, four years before admission, was marked by dyspnea and edema, but no records of the blood pressure were available. She learned of her high blood pressure two years later, at which time there developed vertigo, orthopnea, palpitation and paresthesia of the right leg. She was hospitalized, and phlebotomy was performed with beneficial results. She improved gradually, but another pregnancy occurred with immediate aggravation of all the symptoms. There were increasing edema, precordial pain, nausea, epistaxis and hemoptysis.

*Physical Examination*—There were marked orthopnea, cyanosis and edema of the face and the extremities. The retinas revealed papilledema, narrow pale arteries and constriction of the veins but no hemorrhage or exudate. The heart was hypertrophied, but there were no murmurs. Slight pulmonary edema was observed. The blood pressure was 240 systolic and 160 diastolic, and the pulse rate was 110 and regular. The reflexes were normal.

*Laboratory Examination*—The specific gravity of the urine varied between 1.016 and 1.027, there was a high trace of albumin and the urine contained granular and waxy casts.

*Course*—The course was progressively downward. The nonprotein nitrogen content rose from 35 mg. per hundred cubic centimeters on admission to 64 mg. three days later. Retinal hemorrhages developed. There was a sudden rise in temperature followed by coma and death.

The clinical diagnosis was pregnancy between the fifth and sixth month, chronic cardiovascular disease (hypertensive) aggravated by pregnancy, cardiac hypertrophy with failure and impending pulmonary edema, arteriosclerosis, and possible terminal cerebral hemorrhage.

*Gross Observations at Necropsy*—The heart was enlarged, weighing 520 Gm. The aortic leaflets were thickened and slightly fused. There was no obvious fibrosis of the myocardium, but there were two hemorrhages near the tip of the anterior papillary muscle. In the anterior descending branch of the left coronary artery and in the circumflex branch were sclerotic intimal plaques. One of those in the left branch was large, it narrowed the lumen and in the fixed preparation a small reddish plug, suggestive of a thrombus, almost completely occluded the lumen. Numerous small, soft, yellowish plaques were present in the aorta and in the great vessels of the neck.

*Kidneys*—The right kidney weighed 200 Gm., and the left, 140 Gm., and the two were practically identical. The capsule stripped easily, and the surface was smooth except over a few old depressed scars at the nutrient vessels. The cortex, which was well differentiated from the medulla, was from 4 to 5 mm. thick and appeared to be slightly paler than normal. The stellate veins were prominent. The striations were distinct. The pyramids were deep red and in sharp contrast to the cortex. The renal arteries did not show much sclerosis.

*Microscopic Observations at Necropsy*—The lumen of the coronary arteries was constricted owing to a thickening of the intima. The blood vessels of the spleen had greatly thickened hyaline walls, some being practically obliterated. About the portal spaces a large number of hepatic cells had become necrotic, and much hemorrhage was present. The arteries in some of these spaces had thickened walls and were somewhat hyalinized, but no thrombosed vessels or syncytial cells were seen. There was nuclear fragmentation in these areas. In some places the entire lobule was hemorrhagic and necrotic, and no normal hepatic cells could be seen. In others there was only a small area of necrosis about a portal vein. The blood vessels of the pancreas did not appear to have thickened walls. The intima of the basilar artery was markedly thickened, somewhat homogeneous and vacuolated and contained some cellular and nuclear debris, lymphocytes and mononuclears, fibroblasts and lipid-containing cells. The media and adventitia showed no abnormalities.

*Kidneys* The glomeruli were relatively avascular, and some appeared to be more fibrotic than usual. Few of them, however, were adherent to Bowman's capsule. A number of blood vessels had thickened walls and some appeared to be hyalinized. A few contained hyaline thrombi. The epithelium lining the tubules was fragmented, and a number of purplish-staining concretions were seen in the tubules. The tissue between the tubules appeared somewhat congested. The pelvis of the kidney appeared normal. An elastic tissue stain showed some small blood vessels to have thickened walls, which was evidence more of muscular hypertrophy than of sclerosis.

*Anatomic Diagnosis*—This was moderate generalized arteriosclerosis, cardiac hypertrophy, fibrosis of the myocardium, infarct of the papillary muscle of the left ventricle, necrosis of the liver, with eclampsia, hemorrhage into the mucosa of the colon and urinary bladder, and arteriosclerotic scars of the kidney.

*Summary*—This was a case of a woman of 45 in whom hypertension was aggravated during her fifth pregnancy to the point of cardiac failure. From the clinical point of view death appears to have been the result of failing circulation, and anatomically the coronary, the splenic and the large cerebral vessels seem to have been the only ones which were definitely sclerotic. The pancreatic and renal arterioles were practically unaffected. The most important feature of the case was the presence of eclampsia-like hemorrhages in the substance of the liver.

The presence of lesions similar to those of eclampsia in the liver of a patient dying of heart failure following hypertensive cardiovascular disease with a history of toxemia of pregnancy four years previously is of special interest. The possible vascular basis of such lesions and their relation to the circulatory disease later found in over 50 per cent of examples of eclampsia and preeclampsia deserve notice.

*CASE 3—History*—M. M., aged 29, an American multipara, was admitted to the hospital on Aug. 28, 1930, and died on September 11. The patient had quinsy in 1924, and albumin was found in the urine in the course of an examination for life insurance in 1919. She had been married for four and a half years, but there were no symptoms until the sudden onset of eclampsia three years before death in the seventh month of her first pregnancy. No antepartum blood pressure readings or urinary findings were recorded. A forced delivery was made at the New York Nursery and Child's Hospital, but the blood pressure did not decline afterward. During the follow-up, gradual improvement appeared to take place, but hypertension, headache, palpitation and occasional edema continued. A year before



admission to the Presbyterian Hospital the patient again became pregnant and experienced a spontaneous miscarriage in the third month at the Flushing Hospital. Subsequently she felt fairly well until two weeks before admission to the hospital, when her vision became impaired and there was accompanying headache with frequent dyspnea, palpitation, vomiting and diarrhea.

*Physical Examination*—The patient presented a pale and pasty appearance. Retinal examination revealed blurring of the optic disks, narrowing of the vessels, arteriovenous compression and patches of pigmented scarring which suggested former hemorrhages. The breath was ammoniacal. The heart was enlarged and revealed gallop rhythm and a loud and ringing aortic second sound. The blood pressure was 230 systolic and 145 diastolic. The clinical diagnosis was chronic nephritis, hypertension, arteriosclerosis, uremia and well marked secondary anemia.

*Laboratory Examination*—The examination revealed hemoglobin, 52 per cent, erythrocytes, 3,200,000, blood urea, 1.03 Gm per liter, and creatinine 0.6 Gm per liter. The patient became more restless and irrational, with bilateral choking of the optic disks and a pericardial friction sound. The blood urea rose to 2.25 Gm per liter. The urine showed a trace of albumin in all specimens, with the specific gravity never over 1.010. The patient died with hyperpyrexia.

*Gross Observations at Necropsy*—The heart weighed 340 Gm. The left ventricle was hypertrophied, and the endocardium was thickened. Both coronary arteries showed atheromatous plaques without encroachment on the lumen. In the aorta were small raised atheromatous plaques. The lungs showed bronchopneumonia at the bases.

*Kidneys* The right kidney weighed 50 Gm, and the left, 40 Gm, and the two were practically identical. The capsule stripped easily and revealed a surface covered with pale tan nodules between 1 and 2 mm in diameter, with dark red depressed areas between them. The whole surface of the kidney, both nodules and internodular spaces, was covered with minute transparent spots just large enough to be seen. On section, the cortex was seen to be narrowed and made up of tan colored nodules measuring from 1 to 2 mm with dark red internodular tissue. The whole surface was covered with minute depressions like pinpricks, corresponding to the transparent spots on the surface. The pyramids appeared normal.

*Microscopic Observations at Necropsy*—The muscle fibers of the heart were hypertrophied, and a majority showed striking vacuolation. The intima of the aorta showed thickening with irregular fibrous tissue. There was no fragmentation of elastic tissue. One branch of the coronary arteries showed thickening of the intima. The central arteries of the spleen showed hyaline changes.

*Kidneys* The kidneys were fairly well marked out with radial alternating bands of contrasting structure. The first and most striking was composed of tortuous and tremendously dilated convoluted tubules running from or near the surface of the kidney to varying depths in the medulla. There was no increase of connective tissue between the loops. The alternating bands were narrower and contained connective tissue, blood vessels, tubules and most of the glomeruli. The connective tissue was moderately abundant and loose. It was infiltrated in varying degrees with round cells. In small areas the cellular infiltration was dense, giving the appearance of small abscesses, but there were no polymorphonuclears. Most of the blood vessels were engorged. Many of the arterioles had greatly thickened walls, almost occluding their lumens. The tubules were either not dilated or only moderately so and were predominantly of the type with low cells and dark-staining nuclei. Some contained hyaline plugs. The number of glomeruli appeared to be decreased. Many were partly or completely hyalinized, and some were adherent

to the capsule, the epithelium of which had overgrown their tufts. There was pink-staining material in some of the capsules. There was no typical crescent formation.

*Anatomic Diagnosis*—This was arteriosclerotic atrophy of the kidneys, mild generalized arteriosclerosis, cardiac hypertrophy, fatty heart, myocardial fibrosis and lobular pneumonia.

*Summary*—This was a case of long-standing hypertensive disease apparently antedating several pregnancies. Although the history of repeated infections of the throat and the age suggested chronic glomerular nephritis, the renal lesions were those of arteriolosclerosis and atrophy. There was little to indicate old inflammatory changes in the glomeruli. There was ulcerative colitis which was probably uremic.

The history suggests underlying nephritis. Without the report of the pathologist it would be difficult for the clinician to classify this case which might well be of mixed type. Our studies thus far, however, indicate that in most patients with a history of eclampsia there eventually develops arteriosclerosis with or without arteriosclerotic nephrosclerosis rather than what may strictly be called nephritis.

*CASE 4—History*—M. S., aged 46, an Italian-American, had ten pregnancies. The first eight deliveries occurred at home. The first ended in stillbirth, the seventh in miscarriage and the tenth in missed abortion. The ninth delivery was at the Sloane Hospital for Women in 1924 and was normal. The patient then was 39. During the antepartum period the blood pressure rose three times to 135 systolic. Otherwise nothing of significance was recorded. In the follow-up clinic, in May 1925, six months after she was discharged, the blood pressure was observed to be 210 systolic and 110 diastolic. There was complaint of nausea, cough, vomiting and occasional blurring of vision. At this time the patient was stout, florid and cyanotic. A year and a half later, in December 1926, she was again hospitalized for threatened abortion in her tenth and last pregnancy. At this time her blood pressure was 190 systolic and 112 diastolic, it subsided rapidly to 120 systolic and 76 diastolic after curettage. Retention of nitrogen was not present. The urine showed a very faint trace of albumin. Five years later, in January 1931, she was admitted to the Presbyterian Hospital because of high blood pressure, vertigo, dyspnea and cough.

*Physical Examination*—She presented the picture of circulatory failure and of pulmonary infection. There were cyanosis, dyspnea, edema and evidence of bronchopneumonia at the bases of the lungs. The heart was enlarged, with a mitral murmur. The blood pressure was 200 systolic and 100 diastolic. The urine showed a trace of albumin and granular casts.

The patient died five days after admission.

The clinical diagnosis was bronchopneumonia with cardiac insufficiency, arterial hypertension and chronic nephritis.

*Gross Observations at Necropsy*—There was a moderate bilateral blood-tinged pleural exudate. The heart was enormously enlarged, weighing 760 Gm. The leaflets of the mitral and tricuspid valves were thickened along the line of closure. The endocardium of the left ventricle was thickened and opaque over the papillary muscles and beneath the aortic valve. The coronary arteries showed slight yellow and gray thickening of the intima. The intima of the abdominal aorta showed numerous yellow and gray plaques. The lungs showed bilateral bronchopneumonia.

The pulmonary vessels had numerous yellow and gray intimal plaques. The spleen had prominent blood vessels. The lobulations of the liver were distinct and presented as dark brown areas surrounded by grayish-yellow bands. On section the parenchyma had a nutmeg appearance with large red central zones surrounded by yellowish-gray portal areas. Occasional yellow round areas about 1 cm or more in diameter were seen. The parenchyma of the pancreas appeared to be yellowish pink, spotted with tiny glistening points.

**Kidneys** The organs resembled each other. The right kidney weighed 170 Gm, and the left, 160 Gm. The capsule stripped with difficulty and left a gray granular surface in which were several large depressed scars. The striations were not obliterated. The glomeruli stood out as tiny specks the size of a pinpoint. The pyramids had distinct radiations and congested vessels. The arcuate arteries were rather prominent.

*Microscopic Observations at Necropsy*—The intima of the aorta was thickened and hyalinized in its inner portion, the elastic tissue fibers were increased in number and many were fragmented. A branch of the aorta showed a thickened intima in which were many delicate elastic tissue fibers. The arterioles of the lung had a slightly thickened intima, and those of the spleen were strikingly thickened, at times by hyalinization and again by laminated and vacuolated tissue, but mainly they showed a grayish-yellow swelling of the intima which extended through the wall of the vessel. The smaller arteries of the spleen had thickened and hyalinized intima. The capsule of the liver was thickened, and the lobulations were destroyed. In and about the central areas was considerable congestion, with disappearance by atrophy of the hepatic cells. The portal areas had an increased amount of connective tissue. The lymphatic vessels were prominent. The arterioles showed changes similar to, but not as advanced as, those in the spleen. The capsule of the left suprarenal gland was thickened. The small arteries had hypertrophied muscle cells and slightly thickened intima with occasional hyaline degeneration. In the right suprarenal gland only small masses of lipid-containing cortical tissue surrounded by thick layers of dense fibrous connective tissue were found embedded in a loose connective tissue stroma which was infiltrated by lymphoid and wandering cells. By the Moeller method (fixation and decalcification) a section showed purple-staining calcified masses embedded in connective tissue. The arterioles and small arteries had thickened and hyalinized intima. There was no medullary tissue.

The capillaries of the ovary were engorged, and the small arteries had thickened and hyalinized intima. In the pancreas some increase in interlobular tissue was found. The arterioles showed changes similar to those seen in the spleen. The capillaries were engorged. The arterioles of the stomach had thickened intima, and there were some hyaline deposits in the lymphoid areas.

**Kidneys** A pink granular or fibrinous precipitate was present in many of the glomerular spaces. One glomerulus showed adhesion with its capsule and a focal hyalinization of several loops which was covered by proliferating epithelium of the capsule and tuft. The arteriole of this tuft was thickened and hyalinized, and a short distance from it was a similar vessel the lumen of which was obliterated. Most of the arterioles were like this one and showed an increase of connective tissue in the intima. The tubules contained hyaline, granular and epithelial cell casts. The small arteries had thickened intima, and several had obliterated lumens. The capillaries were engorged.

*Anatomic Diagnosis*—This was arteriolosclerosis of the kidneys, spleen, pancreas, stomach and liver, generalized arteriosclerosis, cardiac hypertrophy and

dilatation, fibrosis of the myocardium, confluent bronchopneumonia, atelectasis, hydrothorax, chronic congestion of the lungs, liver, spleen, pancreas and kidneys, fibrosis and calcification of the right suprarenal gland, and fibrous peritoneal adhesions

*Summary*—This was a case of hypertension which was known to have existed for three years, with marked cardiac hypertrophy and characteristic arteriolar changes in the spleen, pancreas, kidneys and stomach. The patient died of intercurrent bronchopneumonia, and although there was histologic evidence of early lesions in the kidney there was no clinical evidence of renal insufficiency.

*CASE 5—History*—A M, aged 47 years, German-American, was a multipara. Four children were living and well. The patient had had four miscarriages. All the deliveries except the last occurred at home. No record of the blood pressure or of the urinary findings was obtainable. The personal history was irrelevant until 1924 when she was treated for hypertension and nephritis at the Harlem Hospital. The patient was first admitted to the Sloane Hospital for Women on July 14, 1925, as presenting an emergency case. She was in the seventh month of pregnancy and had hypertension, enlargement of the heart, vascular and possible albuminuric retinitis and edema of the face and ankles. The blood pressure was 210 systolic and 136 diastolic. An examination of the blood revealed no retention of nitrogen. The urine contained from 10 to 18 per cent of urinary albumin by volume, and acetone, diacetic acid and finely granular casts. On July 23 there was induced delivery of a premature living baby. The patient was discharged on August 26 with the blood pressure 212 systolic and 164 diastolic and albumin in the urine varying from a faint to a high trace. The Wassermann reaction of the blood was positive. During the follow-up period the patient complained of headache, vertigo and dyspnea, and edema was present. Marked sclerosis of the retinal vessels was noted. There was serious caries with infected gums. Cardiac hypertrophy was present, and the blood pressure was 220 systolic and 160 diastolic. She received antisyphilitic treatment throughout 1930 and 1931. In January 1930 she had a brief attack of aphonia and hemiplegia. She was admitted to the Presbyterian Hospital on Sept. 28, 1931, with an aggravation of the previous symptoms.

*Laboratory Examination*—The blood urea was 0.42 and the creatinine 0.24 Gm per liter. There was a faint trace of albumin in the urine as well as a few hyaline and granular casts. The blood pressure was 238 systolic and 140 diastolic.

The patient became restless, irrational and incontinent and died suddenly on October 6.

The clinical diagnosis was hypertension, cardiac hypertrophy and insufficiency, chronic myocarditis, general arteriosclerosis, syphilis, dental caries, external hemorrhoids, and varicose veins of the internal saphenous system.

*Gross Observations at Necropsy*—The left pleural cavity contained 1,500 cc of dark red fluid and clotted blood, the right cavity contained 50 cc of clear lemon-colored fluid, and a similar amount filled the pericardial sac. The heart weighed 780 Gm. The larger coronary arteries appeared to be tortuous. In general the endocardium was normal. The left ventricle was markedly dilated. There was a little thickening of the endocardium over the septum with subendocardial hemorrhages. The coronary arteries were not narrowed, although atheromatous plaques were scattered along the larger branches. The mediastinal connective tissue about the aorta was filled with a dark red clot of recent origin and enclosed the aorta and esophagus and bulged into the left pleural cavity. The aorta presented many gray and yellow atheromatous plaques. These were especially marked about the arterial ostia, a few were superficially ulcerated. The intima was wrinkled. A crescent-shaped

slitlike opening through the intima and media was present on the posterior wall of the aorta beneath the orifice of the ductus arteriosus. In this zone the media split readily. The splenic artery along the body of the pancreas was unusually tortuous and presented yellow atheromatous plaques. The pancreas was somewhat atrophied.

**Kidneys** The left kidney weighed 140 Gm, and the right, 150 Gm. The capsule stripped easily, leaving an irregular, coarsely nodular surface in which stellate vessels were conspicuous. There was an occasional thin-walled cyst filled with clear lemon-yellow fluid. There were small irregular, shallow depressions on the outer surface. On section, a narrowed cortex was seen which averaged from 4 to 5 mm across. The cortical markings were somewhat obscure, but the glomeruli stood out as conspicuous bright red dots. The medulla, except for congestion, appeared to be normal. The main renal artery was not unusual.

*Microscopic Observations at Necropsy*—The fibers of the heart muscle were hypertrophied and frequently contained vacuoles. There was some slight replacement fibrosis. The intima of the aorta was slightly and uniformly thickened. The media was unusually thick and contained many nuclei. The aorta presented no evidence of syphilis. The main lesion in the aorta consisted of areas of nuclear depletion. In other areas there was definite and striking hypertrophy of the muscle with irregular splits at times extending across the media in steplike fashion. The elastic tissue was markedly fragmented, beaded and disarranged in some sections. The lung showed an occasional thick-walled arteriole, and the splenic arterioles were thick-walled. In the pancreas many of the arterioles were thick-walled and some were completely obliterated.

**Kidneys** Several narrow linear zones were present in the cortex in which there was a small excess of connective tissue. The tubules in these areas were usually lined with basophilic cells having large, vesicular, deeply-staining nuclei. There were also present in these areas completely obliterated hyalinized glomeruli. There was often a small amount of lymphocytic reaction in the scarred areas. The small arterioles were partly obliterated by an intimal proliferation of connective tissue. Eosinophilic material was often seen outside the intima. Some of the smaller arteries showed a similar change.

*Anatomic Diagnosis*—This was generalized arteriosclerosis, arteriolosclerosis of the spleen, kidneys and pancreas, cardiac hypertrophy and dilatation, and dissecting aneurysm of the aorta.

*Summary*—This was a case of a woman who was admitted twice to the hospital with hypertension as the essential clinical finding, together with cardiac hypertrophy and albumin and casts in the urine. The Wassermann reaction was positive. Death was sudden. The essential observations at autopsy were mild arteriosclerosis, arteriolosclerosis involving especially the kidneys, cardiac hypertrophy, and rupture of the aorta at the isthmus with the formation of a dissecting aneurysm.

*CASE 6—History*—E. B., aged 42, a Negress, was a multipara. She was last admitted to the hospital on Feb. 11, 1933, and died on February 22. In 1918 the patient had an uncomplicated, precipitate delivery of a living infant at the Sloane Hospital for Women. Later in the same year there was a miscarriage followed by curettage. In 1919 a forceps delivery of a living child at home was accompanied by hemorrhage. There was a miscarriage in 1922, and in 1924 a normal delivery occurred at the Sloane Hospital for Women, at which time syphilitic changes in the placenta were recorded. The maximum blood pressure at this time was 126 systolic and 90 diastolic. There was a trace of albumin in the urine ranging from faint to high. In 1925, in the follow-up, a heavy trace of albumin

was found. In the same year there was a spontaneous miscarriage followed by curettage. In the following year the blood pressure was 156 systolic and 110 diastolic, a faint trace of albumin was found in the urine, and there was definite retinal arteriosclerosis. In 1928 a normal delivery occurred at the Sloane Hospital for Women. During the pregnancy there was no rise of the blood pressure above the normal and no albumin was present until just before delivery when there was a high trace. In the follow-up clinic in 1929 an examination revealed a blood pressure of 214 systolic and 118 diastolic and an evident increase in the arteriosclerotic changes. In the same clinic in May 1930 the patient complained of headache and vertigo. The retinas revealed marked vascular changes. At that time there was a faint trace of albumin in the urine, and the blood pressure was from 180 to 200 systolic, and 130 diastolic. The patient was obese. In December 1930 the patient was again pregnant. In the sixth month the blood pressure was 200 systolic and 104 diastolic. A faint trace of albumin was present in the urine. Headache, nausea and vomiting were among the symptoms. Supravaginal hysterectomy was performed, and two months later the patient was free from symptoms, the blood pressure being 130 systolic and 80 diastolic. One month later there was a return of palpitation and headache. The blood pressure was 240 systolic and 126 diastolic. The retinal vessels showed sclerosis, there were marked cardiac hypertrophy, a soft systolic murmur and an accentuated aortic second sound. Antisyphilitic treatment was begun on April 1, 1931, because of two weakly positive, and in spite of several negative, Wassermann reactions. In June 1932 there was severe headache. The blood pressure was 230 systolic and 150 diastolic. In February 1933 weakness was increased to the point where housework was impossible. Nausea, vomiting, dyspnea, orthopnea and one attack of acute mania occurred. The maximum blood pressure was 265 systolic and 145 diastolic. The retinas showed flame-shaped hemorrhages with marked narrowing of the retinal vessels and arteriovenous constriction. The heart was enlarged, with gallop rhythm and an accentuated aortic second sound. There was edema of the ankles and legs and moderate anemia. The nonprotein nitrogen content of the blood rose to 100 mg per liter. A trace of albumin was found in the urine, which had a specific gravity of 1.017. The electrocardiogram revealed evidence of myocardial damage. There developed a pericardial friction rub, and the patient died in a state of uremia on February 22.

*Gross Observations at Necropsy*—The heart weighed 480 Gm. There was serofibrinous pleurisy. The cavities of the heart seemed dilated. There was patchy thickening of the endocardium with a few subendocardial hemorrhages. The myocardium of the left ventricle was thickened. There was a beginning fusion of the aortic cusps at the commissures. The papillary muscles were hypertrophied. The coronary arteries showed small yellow intimal plaques, and the aorta, a few, small, slightly raised intimal plaques. In the spleen the vessels stood out prominently. The brain revealed no changes.

*Kidneys* The two organs were identical, the left weighing 130 Gm, and the right, 190 Gm. The capsule stripped easily, exposing a diffusely granular surface on which there were innumerable small, slightly raised, yellowish areas and many small areas of hemorrhage ranging from the size of a pinpoint to several millimeters in diameter. Fetal lobulations were present. In many areas the boundary between the cortex and the medulla was no longer distinct. Numerous small, irregular yellowish areas and small areas of hemorrhage were seen on the cut surface. Two distinct kidney pelves were present in each kidney, both were injected, and small hemorrhages were seen in the mucosa of each. Two ununited ureters were also present in each kidney.

*Microscopic Observations at Necropsy*—The myocardial fibers were hypertrophied. A few of the small branches of the coronary vessels showed intimal thickening, and one was obliterated. The intima of the aorta was thickened by fibrous connective tissue, some of which appeared to be hyalinized. The muscular coats of a moderate-sized artery of the adventitia were atrophic and revealed some thickening of the intima. The internal elastic coats were reduplicated and in some areas showed fragmentation. Calcium was not present. The walls of the central arterioles of the spleen were markedly thickened and hyalinized. Many of the lumens were completely obliterated. The internal elastic lamella of many of the central arterioles was straightened, reduplicated and fragmented. In a few of the small vessels only small fragments of elastic tissue remained. There was intimal thickening of the arterioles of the portal areas of the liver. The pancreas showed atrophy of some of the acini and revealed fibrous replacement with marked increase of the interlobular tissue. There were marked thickening and hyalinization of the walls of the arterioles, many of which were completely occluded and some of which contained a few dark blue granules, probably calcium. In some of the arterioles, particularly those which were completely occluded, very little elastic tissue remained. In others the internal elastica was straightened, reduplicated and fragmented. In the larger vessels the changes were not marked. The increased fibrous tissue was well marked.

*Kidneys* The small and medium-sized arteries showed considerable intimal thickening, and most of the arterioles, including those entering the glomeruli, showed marked thickening of their walls with hyalinization and partial or complete occlusion of the lumens. Some of the necrotic arterioles were infiltrated with polymorphonuclear and mononuclear cells and contained cellular debris. No normal-appearing arterioles were seen. A few essentially normal glomeruli were seen, but most of them showed from moderate to markedly advanced changes. Comparatively few completely hyalinized or collapsed glomeruli were seen. The glomeruli showed a variety of lesions: hemorrhage, congestion and hyalinization. The arteries showed straightening, fragmentation and occasional reduplication of the internal elastica. In many of the occluded arterioles practically no elastic tissue remained.

The suprarenal glands showed moderate thickening of the arteriolar walls in the connective tissue outside the capsule. The cortical cells appeared to contain an abundant amount of lipoid. The capillaries were congested. Several of the arterioles in the deep portion of the cortex were completely occluded by hyalinized fibrous tissue. In a few of the arterioles outside the capsule the internal elastica was fragmented. In most of them it appeared to be normal, however, and the thickening of the wall involved chiefly the middle coat. In the occluded arterioles of the cortex no elastic tissue remained.

*Anatomic Diagnosis*—This was generalized arteriosclerosis, arteriolar nephrosclerosis, cardiac hypertrophy and dilatation, clinical uremia, calcium deposits in the lungs, slight arteriosclerosis of the aorta, fibrosis of the myocardium, acute fibrinous pericarditis, chronic passive congestion of the liver, lungs and spleen, and fibrous peritoneal adhesions.

*Summary*—This was the case of a Negress who had many pregnancies and miscarriages and a long history of hypertension. She was probably syphilitic. She died in a uremic state, with cardiac failure. The arteriolar lesions were of the acute necrotizing type and were especially well shown in the kidneys, the pancreas, the spleen and the suprarenal glands. In the kidneys there was moderate secondary atrophy, and in the pancreas there was diffuse fibrosis, probably

as a result of the arterial change. The coronary vessels seemed to have been spared, and the myocardium showed little change other than hypertrophy. The renal lesions, on closer study, gave the impression of a more complex change than that due merely to the vascular disease. We are inclined to associate the tubular changes with the effects of the intensive antisyphilitic treatment. The hypophysis, in the single section examined, showed definite proportional decrease of the oxyphil cells and an increase in the basophil element similar to the change described in cases of hypertension by Krause. Another interesting feature was the extensive calcification of the pulmonary veins and alveolar septums.

*CASE 7—History*—C. D., aged 67, an American, was admitted to the hospital on Oct. 17, 1933, and died on October 20. The patient was admitted because of a swelling in the right lower quadrant of the abdomen with dull pain, which had been present for several weeks. There was a history of scarlet fever at the age of 10 years, followed by cardiac disturbance and deafness. During the few years prior to admission dyspnea and palpitation on exertion, occasional edema of the ankles and high blood pressure had been noted. The patient was married in 1893 and had five pregnancies. The first and fourth resulted in stillbirth at term and the fifth in a spontaneous abortion. Eclampsia occurred with the first pregnancy in 1896.

*Physical Examination*—The patient was a feeble, poorly nourished woman of 67. Bilateral deafness was present. The left side of the heart was enlarged, and there were forceful impulse, systolic shock and a short systolic murmur at the apex. The rate was irregular from premature contractions. The blood pressure was 170 systolic and 95 diastolic. There was an evident mass in the right lower quadrant of the abdomen. Pretibial edema was present. The cell count and the nonprotein nitrogen content of the blood were normal. Two days after admission the patient was found aphasic and dyspneic with a fibrillating heart. Death which occurred an hour later was thought to be due either to cerebral accident or to heart failure.

The clinical diagnosis was right ovarian cyst, chronic cardiovascular disease, mitral stenosis and insufficiency, and cerebral hemorrhage.

*Gross Observations at Necropsy*—A large cyst containing 4,000 cc of cloudy yellowish fluid was found in the right ovary. The heart weighed 330 Gm. There was thickening of the mitral valve with a few vegetations near the line of closure. The cusps of the aortic valve were slightly adherent at the commissures. Small yellowish atheromatous patches were found in the ascending aorta. The left coronary artery showed several arteriosclerotic patches. The lungs revealed nothing significant, and no abnormalities were noted in the arteries of the spleen, liver, pancreas or suprarenal glands.

*Kidneys*. The kidneys were identical. Each weighed 150 Gm. The surface was nodular. The remains of fetal lobulations were seen, and in addition there were rather large scars and a number of cysts. The capsule stripped with difficulty and pulled away a little of the kidney tissue with it, leaving a finely granular surface with a number of cysts and some irregular scars. The cortex was reduced in size. The glomeruli could be seen, but the striations were indistinct. The blood vessels were slightly sclerotic.

The brain was not examined.

*Microscopic Observations at Necropsy*—There was slight thickening of the mitral valve, which had become hyalinized and at one point calcified. There was some polymorphonuclear infiltration. The media of the aorta showed rarefaction, vacuolation and degeneration of the nuclei. The adventitia was normal. The lungs were moderately congested. The spleen showed no change and the suprarenal glands and the pancreas were normal.



**Kidneys** The kidneys showed small cortical scars containing atrophied tubules and sometimes hyalinized glomeruli. No glomerular adhesions were present. The blood vessels showed thickened walls.

*Anatomic Diagnosis*—This was arteriosclerosis of the aorta, senile arterionephrosclerosis, patent foramen ovale, acute endocarditis—chorda tendineae of the mitral valve, cystadenoma of the right ovary, tuberculosis of the bronchial lymph nodes, miliary tuberculosis of the liver, infarcts of the lungs and phleboliths of the spleen and the accessory spleen.

*Summary*—The valvular lesions are not significant. The patient may have died of a cerebral accident, but this could not be verified.

It is possible that senile arteriosclerosis accounts for this picture entirely. The previous eclampsia cannot, however, be ignored as a possible contributory factor in the vascular changes.

The nephritic group comprises 4 cases.

*CASE 8—History*—R. R., aged 28, an American-born Jewess, was a primipara. She was first observed in the outpatient department of the Sloane Hospital for Women on Dec. 24, 1924, in the early weeks of pregnancy. Scarlet fever, diphtheria and an injury to the spine which caused lateral curvature were experienced in childhood.

The blood pressure was normal. The urine was of low specific gravity and showed a heavy trace of albumin. On June 5, 1925, the blood pressure had risen to 150 systolic and 112 diastolic. On this account the patient was admitted to the ward. Here she presented no evidence of infection and none of cardiovascular disease. Albuminuria persisted, suggesting an underlying renal lesion. Several admissions to the hospital followed during the subsequent six months because of persistent albuminuria and occasional hypertension. She was delivered of a normal infant on June 10, 1925. In the follow-up, in 1926, there was complaint of weakness. A physical examination revealed blood pressure of 136 systolic and 90 diastolic and some sclerosis of the larger vessels and edema of the ankle. Albuminuria persisted. In 1928 the edema increased. The albumin was 20 per cent by volume, and many finely and coarsely granular casts were present. The blood pressure was 146 systolic and 110 diastolic. The patient was admitted to the hospital of the Rockefeller Institute several times, where in May 1930 the blood pressure was noted to be 218 systolic and 132 diastolic. Secondary anemia was present, and there were purpuric spots on the extremities. There was marked retention of nitrogen. Albumin, blood and casts were present in the urine. In May 1931, on the final admission to the last-mentioned hospital, there was complaint of blindness. Serious albuminuric retinitis was found. The blood pressure was 260 systolic and 164 diastolic. The excretion of phenolsulphonphthalein was but a faint trace in two hours. The test for urea clearance showed a result about 6 per cent of normal. Death occurred from uremia on June 15.

The clinical diagnosis was chronic nephritis, cardiac hypertrophy and uremia.

*Gross Observations at Necropsy*—The heart weighed 400 Gm., but otherwise it was normal. The spleen, liver, pancreas and suprarenal glands were normal. The left kidney weighed 100 Gm., and the right, 150 Gm. The capsules of the kidneys did not evert when cut and were stripped off with difficulty, leaving a granular surface. The cortex averaged about 4 mm. in thickness.

*Microscopic Observations at Necropsy*—**Kidneys** Sections stained with eosin and methylene blue showed marked distortion of the renal architecture. The

glomeruli just beneath the capsule were as a rule normal except that they were enlarged. The glomeruli farther in showed all the variations of destruction. Practically all showed one or more adhesions between the capsular and the glomerular epithelium. The connective tissue forming the capsule was increased in thickness. Some glomeruli were almost completely hyalinized, leaving only a few nuclei visible, others showed a few capillary loops remaining. The tubules varied. Some were increased in size owing to hypertrophy of the cells lining the tubules, others were atrophied, many contained hyaline casts, and many contained the shadowy outlines of red blood cells. Some tubules were completely obliterated by scar tissue. The blood vessels were engorged with red blood cells. A few of the larger arteries showed some thickening of the media. Sections showed a wrinkled basement membrane in the glomerulus and around the tubules. Numerous masses partly of intercapillary fibers were seen. Many of the glomerular loops were compressed by this means and also by an increase in the endothelial cells.

*Anatomic Diagnosis*—This was chronic nephritis, cardiac hypertrophy, acute bronchitis and generalized anasarca.

*Summary*—This was the case of a woman under 30 in whom nephritis was discovered first during pregnancy. This might have been of scarlatinal or of diphtheritic origin. In spite of persistent albuminuria and mild hypertension pregnancy was successfully terminated. During a follow-up period of six years there was a gradual increase in symptoms of renal insufficiency, and the patient died of uremia. Gross and microscopic observations revealed evidence of chronic nephritis.

*CASE 9—History*—E. K., aged 37, an American, was a primipara. Renal disturbance was discovered at the age of 17 after several attacks of sore throat. During the sixth month of her first and only pregnancy, in 1921, without previous symptoms, coma occurred suddenly with convulsions. Abortion was induced. After an interval of five years without symptoms headache, nausea, vomiting and visual disturbances appeared with a rise in the blood pressure and retention of nitrogen. After a variable course there was an infection of the respiratory tract followed by generalized edema, dyspnea and blurring of vision. She was first admitted to the hospital on Jan. 3, 1929, and was discharged improved on January 20, was readmitted on May 23 and died suddenly on May 28.

*Physical Examination*—The heart was enlarged. The blood pressure was 250 systolic and 140 diastolic. Ecchymoses were present over the surface of the skin. The fundi revealed arteriosclerosis with fresh hemorrhages. There was marked anemia, and urine of low specific gravity showed a high trace of albumin and casts. General anasarca and signs of pericarditis developed before death. The clinical diagnosis was chronic nephritis, uremia, hypertension, cardiac hypertrophy, and serofibrinous pericarditis.

*Gross Observations at Necropsy*—The heart weighed 450 Gm. The pericardium was covered with shaggy fibrinous exudate in which were small hemorrhages.

*Kidneys*—The left kidney weighed 150 Gm., and the right, 160 Gm. The capsule stripped with difficulty, leaving a pebbly surface. On the cut surface it was difficult to distinguish between the cortex and the medulla, where the distinction was possible the cortex was not more than 2 mm. thick. The markings on the cut surface were irregular. There were a few punctate hemorrhages. The blood vessels on the cut surface were not prominent.

*Microscopic Observations at Necropsy*—The capsule was thickened and torn. Beneath it were several small scars. The glomeruli showed various stages of

degeneration, some with only slightly thickened capsules or adherent tufts, some completely hyalinized and others atrophied. Hyaline changes had occurred in some of the intraglomerular capillaries. The tubules varied greatly in size, polymorphonuclears were present in some. The interstitial tissue was increased and contained small collections of lymphocytes. The smaller vessels had slightly thickened walls. The elastic laminae of the vessels were reduplicated.

*Anatomic Diagnosis*—This was chronic intracapillary glomerulonephritis, cardiac hypertrophy, acute organizing fibrinous pericarditis, bilateral hydrothorax, acute congestion of the spleen and the liver, patent foramen ovale, general mild arteriosclerosis, and moderately advanced sclerosis of the coronary arteries.

*Summary*—This was a case of chronic glomerulonephritis of the intracapillary type with terminal pericarditis in a woman with a history of a convulsive pregnancy twelve years before.

*CASE 16—History*—G. S., aged 38, an American, was a primipara. She was admitted to the hospital Jan. 22, 1931, because of persistent hypertension, albuminuria and retention of nitrogen. There was a history of scarlet fever and pneumonia in early life. In 1928, in the fifth month of her only pregnancy, evidence of renal difficulty was discovered. The blood pressure was 170 systolic and 90 diastolic. Edema of the back and lower extremities was present. The urine contained a large amount of albumin, and the nonprotein nitrogen content of the blood was slightly elevated. A stillborn child was delivered, after which the patient was hospitalized because of pyelitis. The anasarca vanished. The blood pressure fell to 118 systolic and 90 diastolic. Ten days after discharge the blood pressure was 154 systolic and 90 diastolic. Albuminuria persisted, and the urine was of low specific gravity. The eyegrounds were normal. Gradually moderate secondary anemia developed, and the nonprotein nitrogen level rose to 114 mg per hundred cubic centimeters of blood. In January 1931 the patient was emaciated and pale. There was moderate general arteriosclerosis. The retinal arteries were small, and several minute white patches were noted. The patient was discharged unimproved at her own request on February 1, and was readmitted on June 26 because of orthopnea, dyspnea, cough, epistaxis, nausea, vomiting and palpitation following a "cold."

*Physical Examination*—The blood pressure was 170 systolic and 100 diastolic. General anasarca, uremic breath and a pericardial friction rub were noted. The hemoglobin content was 32 per cent, and the red blood cells numbered 1,700,000. The blood urea was 40.7 mg, and the creatinine, 7.5 mg per hundred cubic centimeters.

The patient died on July 31.

The clinical diagnosis was chronic nephritis, uremia, hypertension, secondary anemia, and pericarditis.

*Gross Observations at Necropsy*—All the serous cavities showed exudate. The heart was enlarged and weighed 420 Gm. The epicardium was roughened and thickened. The coronary arteries showed some yellow plaques without occlusion. Atheromatous plaques were present in the aorta. The liver, spleen, pancreas and suprarenal glands were normal.

*Kidneys*—The left kidney weighed 30 Gm, and the right, 15 Gm. The capsule stripped with difficulty, leaving a pale, rough granular surface. The cortex was from 3 to 4 mm wide, and a few glomeruli were visible. An unusual number of large arteries were visible in the cortex. The pyramids were comparatively large. The striations were seen with difficulty and were for the most part regular.

The pelvis was of normal size and presented a pale mucosa which was studded with minute yellow cysts and a few petechial hemorrhages. The peripelvic fat was increased. The right kidney was similar to the left, the cortex was smaller, measuring from 1 to 2 mm in width. In a few instances the pyramids were absent and the calices extended to the capsule. No glomeruli were visible.

*Microscopic Observations at Necropsy*—The cortex bore numerous completely hyalinized glomeruli. Other glomeruli showed only partial hyalinization with adhesion of various loops to Bowman's capsule. Their tufts were large and there appeared to be an increased amount of connective tissue binding several contiguous loops together. A few unaffected glomeruli remained near the periphery. Many of the tubules had disappeared and were replaced by connective tissue. These areas were near the completely hyalinized glomeruli. The majority of the remaining tubules were grouped in islands associated with the glomeruli which were still functioning. They were dilated and lined by low cuboidal or flattened epithelium. Their lumens were filled with pink granular material, and hyaline and granular casts plugged some of the smaller tubules. When the dilated tubules were near the surface they projected considerably above its level. The stroma was greatly increased and was highly cellular, the cells being chiefly small round cells. The arterial walls were markedly thickened. There was a pronounced increase in the amount of elastic tissue of the walls of the smaller arteries. In another section few glomeruli were seen, but those present were large, with hypertrophied tufts and only occasional hyalinization of a loop. There was less stroma throughout the section, the tubules being present in larger numbers, dilated and tortuous. Near the pelvis was congestion of the capillaries, and a few of the tubules were completely plugged with polymorphonuclear leukocytes. They were found in the interstitial tissue in one isolated clump associated with small round cells and slight edema.

*Summary*—This was a case of chronic glomerulonephritis with uremia and hypertension. One of the sections of the kidney showed acute pyelonephritis which was probably fatal. The pericarditis was probably due to the uremia.

*CASE 11—History*—L. Z., aged 29 years, German, was a primipara. Her history was irrelevant until the onset of the first pregnancy, which was marked by early vomiting and headache. On March 3, 1931, in the fourth month of pregnancy, the patient was admitted to the hospital as presenting an emergency case.

*Physical Examination*—There were marked edema of the face and notable cardiac enlargement. The blood pressure was 180 systolic and 90 diastolic. There was moderate enlargement of the liver. The urine contained a heavy trace of albumin and numerous casts. The nonprotein nitrogen content of the blood was 82 mg per hundred cubic centimeters, the uric acid 12.5 mg, and the creatinine 6.4 mg.

On March 26 the fetus was delivered by vaginal hysterotomy. This did not influence the condition. There were increasing retention of nitrogen in the blood and the other evidences of progressing uremia. The patient died on April 2.

The clinical diagnosis was chronic nephritis, hypertension, cardiac hypertrophy, and acute uremia.

*Gross Observations at Necropsy*—The heart weighed 385 Gm. There were a few yellow plaques in the aorta. The spleen, pancreas, liver and suprarenal glands were normal. The left kidney weighed 190 Gm, and the right, 210 Gm. The right kidney showed a double ureter and pelvis. The capsule was somewhat adherent, and the surface was pale and granular. The cortex was decreased in thickness and showed old scars.

*Microscopic Observations at Necropsy*—The blood vessels of the heart were normal. The lungs revealed edema. The sinuses of the spleen were engorged and small hemorrhages were present. The liver was congested but was otherwise normal. The kidneys showed large scars alternating with columns of dilated tubules. In the scars were many fibrotic glomeruli, numerous small lymphocytes and atrophic tubules. Other glomeruli were enlarged and showed numerous adhesions to the capsule of Bowman. In many the capillary loops were obliterated. Many others were in a process of fibrosis, showing adhesions and thick obliterated capillaries. Some tubules were dilated, and some were lined with fragmented columnar cells. A few contained a homogeneous brownish-staining plug which was acellular. There were several large abscesses infiltrated with polymorphonuclear leukocytes and fibrinous material. The tubules in these areas contained many red blood cells. About the pelvis was marked infiltration with lymphocytes and plasma cells. The vessels were sclerotic. The arterioles in another section showed markedly thickened walls.

*Anatomic Diagnosis*—This was subacute glomerulonephritis, cardiac hypertrophy, a puerperal uterus and retained placenta, pulmonary edema, with partial atelectasis of the lungs, abscesses of the kidney, fibrous pleural adhesions, hemosiderosis of the spleen, and congenital malformation of the kidney.

*Summary*—This was a case of subacute glomerulonephritis, the etiology of which was not indicated in the history. With pregnancy there was apparently an exacerbation of a renal lesion which necessitated the termination of the pregnancy. In spite of abortion the symptoms of renal insufficiency continued. The patient died after seven days. There was also a superimposed interstitial inflammation, probably bacterial.

# OXYGEN UTILIZATION AND LACTIC ACID PRODUCTION IN THE EXTREMITIES DURING REST AND EXERCISE

IN SUBJECTS WITH NORMAL AND IN THOSE WITH DISEASED  
CARDIOVASCULAR SYSTEMS

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Adequate information as to the state of the peripheral circulation in health and in various stages of heart disease is lacking. Some investigators<sup>1</sup> still consider that the behavior of the peripheral circulation is entirely dependent on the action of the heart, and that disturbances of this circulation can be regarded as an index of an early stage of heart failure. Eppinger and his co-workers,<sup>2</sup> on the other hand, have claimed that primary changes in the peripheral circulation precipitate failure of the diseased heart. Still other workers have presented evidence indicating that the early clinical manifestations of failure depend, as a rule, on changes in the pulmonary circulation due to cardiac insufficiency. In certain types of heart disease with primary failure of the left ventricle, such as arterial hypertension, arteriosclerosis and aortic insufficiency, a severe degree of disability may be present, with marked alteration in the hemodynamics of the pulmonary circulation but with a normal or only slightly altered peripheral circulation.<sup>3</sup>

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1 Lewis, T. Early Signs of Cardiac Failure of the Congestive Type, *Brit M J* **1** 849, 1930, *Diseases of the Heart*, New York, The Macmillan Company, 1933

2 Eppinger, H., Kisch, F., and Schwarz, H. *Das Versagen des Kreislaufes*, Berlin, Julius Springer, 1927

3 (a) Weiss, S. Circulatory Adjustments in Heart Disease. A Concept of Circulatory Failure, *Ann Int Med* **5** 100, 1931. (b) Robb, G. P., and Weiss, S. Effect of Digitalis and Rest on Pulmonary and Peripheral Circulation in Patients with Circulatory Failure Caused by Heart Disease, *Proc Soc Exper Biol & Med* **29** 1231, 1932, Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure, *J A M A* **100** 1841 (June 10) 1933, The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Disease. Their Relation to Clinical Types of Circulatory Failure, *Am Heart J* **9** 742 (Aug.) 1934

## PURPOSE OF THE INVESTIGATION

In the present study, information as to the behavior of the peripheral circulation in subjects with normal and in those with diseased cardiovascular systems was sought by studying the utilization of oxygen and the production of lactic acid in the upper and lower extremities during rest, while the subject was standing and after exercise. Provided the metabolism is unchanged, the arteriovenous oxygen difference is an index of the flow of blood through the extremity, that is, a decrease in the arteriovenous difference is due to an increase in the blood flow and vice versa. In heart failure the basal metabolic rate is normal or increased. One can therefore interpret an increased arteriovenous oxygen difference in patients with heart failure as evidence of a decreased flow of blood through the extremities. The close interrelation between the supply of oxygen and the formation of lactic acid and the bearing on it of the blood supply to the muscles is suggested mainly by the work of Hill and his associates<sup>4</sup>. It has been suggested that the capacity of the muscles to eliminate the lactic acid formed during exercise depends on the adequacy of the local circulation.

A simultaneous study of the blood flow of the upper and of the lower extremities is of particular interest, since the amount of tissue in the extremities makes up at least from 30 to 40 per cent of the total body tissue and since the circulation within them represents the blood supply to the most important peripheral structures of the body. During and after walking, therefore, changes in the venous blood of the lower extremities represent metabolic alterations in a considerable bulk of active muscle tissue, while blood obtained simultaneously from the relatively passive arms serves as a control and gives information on the state of the relatively inactive tissue.

As an exercise test, we chose stair climbing. It is a natural activity, which involves mainly the muscles of the lower extremities. Other types of muscular work, including bicycle riding, are performed by persons with varying degrees of skill and not always with the same groups of muscles.

## METHOD

The investigative procedure was carried out in the morning, with the subject in the postabsorptive state, as follows. The person rested in the horizontal position, or as nearly horizontal as orthopnea permitted, for at least thirty minutes

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4 (a) Hill, A. V. The Oxidative Removal of Lactic Acid, *J. Physiol.* **48**, 1914. (b) Hill, A. V., Long, C. N. H., and Lupton, H. Muscular Exercise, Lactic Acid, and the Supply and Utilization of Oxygen. III, *Proc. Roy. Soc., London, s. B.* **96**, 455, 1924. (c) Hill, A. V., and Lupton, H. Muscular Exercise, Lactic Acid and the Supply and Utilization of Oxygen, *Quart. J. Med.* **16**, 135, 1922.

Samples of venous blood were then drawn without stasis, under oil, from an antecubital and a femoral vein. The subject then rose, walked 20 feet (6 meters) to an elevator, was carried down two flights of stairs and then walked slowly up two flights (forty-six steps, each  $6\frac{1}{2}$  inches [16.5 cm] in height), walked 20 feet to the bed and lay down, the total procedure taking about two and one-half minutes. Samples of blood from the antecubital and femoral veins were again drawn simultaneously by two operators, immediately after the subject lay down, again after ten minutes and in the case of the femoral blood after twenty minutes also. A sample of arterial blood was also taken under oil, usually from a femoral artery. The heart rate was counted at the apex while the patient was resting and at half-minute intervals after the exercise. The degree of dyspnea and the effort involved in carrying out the exercise were estimated. The venous pressure during rest was determined by the direct method of Moritz and von Tabora,<sup>5</sup> and the vital capacity of the lungs was determined with a Collins spirometer.

In patients with congestive failure so severe as to make the exercise test inadvisable, samples of blood were taken when the patient was at rest and again after two minutes' standing at ease. The blood during rest was drawn in the usual manner, when the patient was standing erect, from a femoral vein and an antecubital vein, with the arm supported approximately horizontally at the level of the heart.

The samples of blood were analyzed for oxygen and carbon dioxide by the method of Van Slyke and Neill<sup>6</sup> and for lactic acid by the method of Friedemann, Cotonio and Shaffer.<sup>7</sup> Duplicate or triplicate determinations were made on each sample. Some of the results of this investigation were presented in 1931.<sup>8</sup>

#### MATERIAL

The seventeen control subjects chosen as "normal" persons were ambulatory patients suffering from a variety of minor complaints, but with no detectable abnormality of the cardiovascular system. There were seventeen patients with organic heart disease who showed compensation, i. e., who had no symptoms or signs of congestive failure and who could perform the exercise test without appreciable distress. Sixteen patients with heart disease had "dry" failure. They had no detectable physical signs of congestive failure of the peripheral circulation and were comfortable while at rest, but all of them had dyspnea to a greater or less extent on performing the prescribed exercise. There were seventeen patients with frank congestive failure, the symptoms varying from a few râles at the bases of the lungs or the slightest edema of the ankles to massive anasarca or extreme respiratory distress while at rest.

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5 Moritz, F., and von Tabora, D. Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f klin Med* **98** 475, 1910.

6 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523, 1924.

7 Friedemann, T. E., Cotonio, M., and Shaffer, P. A. The Determination of Lactic Acid, *J Biol Chem* **73** 335, 1927.

8 Weiss, S., and Ellis, L. B. The Peripheral Circulation in Heart Disease, *J Clin Investigation* **10** 672, 1931.



## EXPERIMENTAL RESULTS

*Oxygen Content and Arteriovenous Oxygen Difference*—The average levels for oxygen in the femoral veins (during rest) in the patients with compensated cardiac disease and in the "normal" subjects were nearly the same (table 1 and charts 1 and 3). This was also true of the arteriovenous oxygen differences. In the two groups of patients with heart failure, particularly in the group with congestive failure, the oxygen contents were lower and the arteriovenous oxygen differences higher. Chart 1 shows the tendency for the patients with congestive failure to have high oxygen differences.

The values obtained for antecubital venous blood were essentially the same as those obtained for the femoral venous blood. There was a slight tendency for the oxygen differences in the leg to be lower and those in the arm to be higher in the group with compensated cardiac disease than in the normal group, but the average for the arm and leg was nearly the same in the two groups. In the patients with failure, the oxygen contents tended to fall and the oxygen differences to rise.

In every case in all of the groups the oxygen content of the femoral venous blood dropped considerably immediately after exercise, and the arteriovenous oxygen difference correspondingly increased (table 1 and chart 1). The average arteriovenous difference after exercise was somewhat greater in patients with cardiac failure than it was in the other groups. This increase was most definite in the group with congestive failure. A comparison of the ranges of values in chart 1 shows that the values for the group with "dry" failure fall within the same range as those for the normal group, although they average slightly higher. The relative increase in the oxygen difference over the resting values, however, tends to be slightly less in the group with congestive failure than in the normal and compensated groups. This was probably due to the fact that the patients with congestive failure utilized the oxygen from their blood to the fullest extent possible, since the average oxygen content of their femoral venous blood after exercise was only 3.7 volumes per cent, and in three of these patients it reached the extraordinarily low level of 2 volumes per cent or less. The lowest oxygen content of the femoral venous blood observed was 1.1 volumes per cent. Obviously, in such patients it was a physical impossibility to increase the oxygen utilization to a greater extent. In all of the groups the femoral venous oxygen had returned to approximately the initial resting value in ten minutes.

The observations on the venous blood drawn from the arm immediately after exercise were similar, in general, to those on the femoral blood. In two cases, however, a control and a patient with "dry" failure, the arteriovenous oxygen difference became less instead of greater.

After standing, the findings in the group of five control subjects and the group of seven patients with congestive failure were similar (table 2). The arteriovenous oxygen difference of the leg increased during the two minute standing period in every case, usually to a marked degree. In every case but one it also increased in the arm, but usually to a less extent than in the leg.

*Lactic Acid*—The range of values and the average for the lactic acid when the subjects were at rest were practically the same in all groups (table 1 and charts 2 and 3).

In the normal subjects after exercise, the lactic acid of the venous blood draining the active exercising tissue, i. e., the legs, rose sharply from its preceding average resting level of 13 mg to 29 mg per hundred

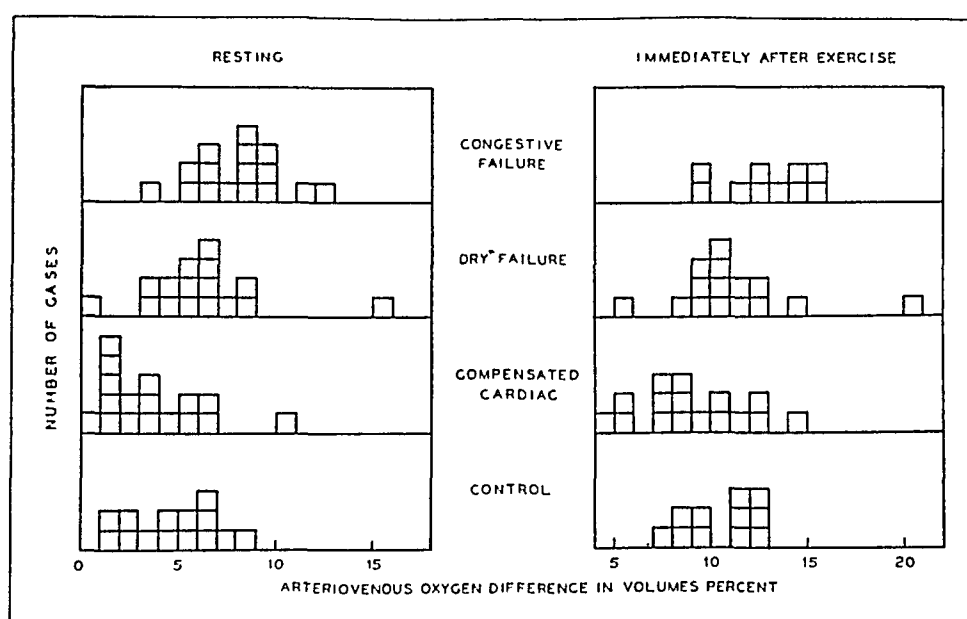


Chart 1—The distribution curves for the individual cases, showing the femoral arteriovenous oxygen differences during rest and immediately after exercise

cubic centimeters (table 1 and charts 2 and 3). It then fell rather abruptly in the first ten minutes and more slowly in the succeeding ten minutes, but did not reach the resting value within this time. The general level of the circulating lactic acid, represented by the antecubital venous blood, rose more slowly than that of the lactic acid coming directly from the active tissue of the leg, but in samples taken after the patient had rested for ten minutes the lactic acid of the venous blood was approximately the same in the arm and in the leg.

The lactic acid of the patients with compensated heart disease showed the same changes as did that of the normal subjects. With increasing degrees of cardiac failure, however, there was a distinct tendency for the femoral lactic acid to rise to higher levels immediately after exercise and then to fall at a slower rate than normal (chart 3). This is shown

TABLE 1—The Ranges and Averages of Various Values in the Peripheral Circulation at Rest and at Intervals After Exercise in the Normal Subjects and in the Patients with Heart Disease

Diagnosis	No of Cases	Venous Oxygen Content, Vol per Cent						Arteriovenous Oxygen Difference, Vol per Cent						Per centage of Saturation of Arterial Blood	Lactic Acid, Mg per 100 Cc						Venous Pres		Vital Capacity, Liters
		Leg			Arm			Leg			Arm				Leg			Arm			Of Om Water	Liters	
		During Rest	After Exercise	Imme diately	During Rest	After Exercise	Imme diately	During Rest	After Exercise	Imme diately	During Rest	After Exercise	Imme diately		During Rest	After Exercise	Imme diately	During Rest	After Exercise	Imme diately			
Control	17	81.69 134	44.11 73	97.16 129	51.14 95	10.88 47	71.12 103	15.65 40	107.9 47	19.12 83	08.14 52	86.96 93	9.16 13	17.44 29	15.35 20	14.23 18	10.17 13	13.24 17	13.23 17	-2 +10 +5	2555 35		
Compensated heart disease	17	62.19 140	33.15 84	56.18 127	27.13 80	08.10 36	41.14 90	12.89 35	24.11 51	48.14 97	26.11 58	83.99 93	8.18 12	19.64 31	14.40 19	14.25 18	9.17 12	14.31 17	14.25 18	-3 +9 +4	2551 33		
Dry" failure	16	69.18 116	30.99 64	68.15 115	26.10 65	06.15 61	51.21 112	14.13 48	05.10 62	28.21 113	25.14 80	90.100 93	9.18 13	25.66 36	16.37 23	13.38 19	9.20 13	13.24 18	14.25 18	-4 +15 +6	2042 23		
Congestive failure	17	42.14 85	11.74 37	38.15 90	17.10 47	34.12 78	07.15 128	14.12 65	11.10 62	45.15 116	05.14 80	86.98 91	10.20 14	24.47 37	20.38 30	17.27 22	9.20 14	12.38 22	13.24 18	+5 +22 +13	0928 19		

\* The averages appear in bold faced type

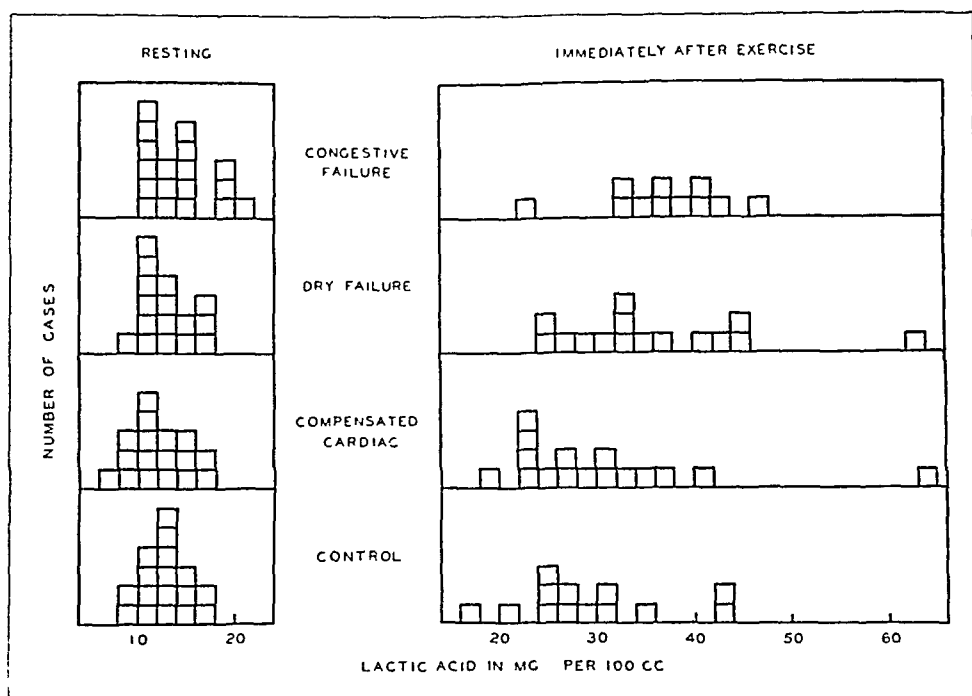


Chart 2—The distribution curves for the individual cases, showing the femoral lactic acid content during rest and immediately after exercise

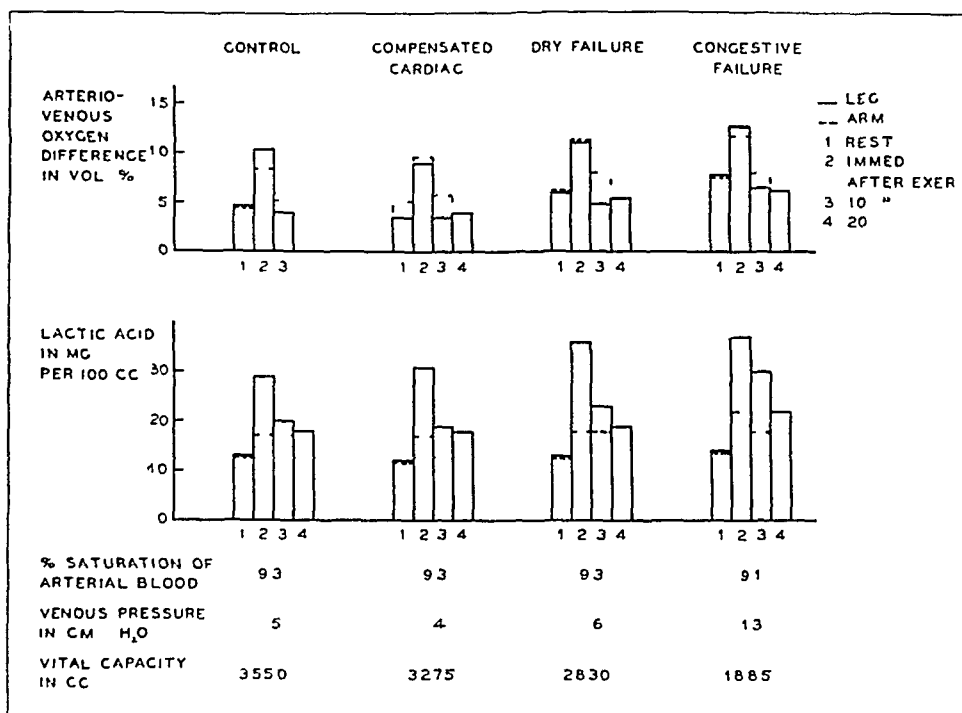


Chart 3—The average values in the various groups for the circulatory measurements of the arm and leg during rest and at intervals after exercise

in the average figures for the groups with "dry" and congestive failure. The upper range of lactic acid values, however, was practically the same in all four groups both immediately and ten minutes after exercise.

Lactic acid determinations were performed on blood from the femoral and antecubital veins taken from five control subjects and six patients with congestive failure while they were erect after standing for two minutes (table 2). The lactic acid values rose on an average of from 1 to 2 mg above the resting level in both the arm and the leg.

*Etiology of the Cardiac Condition and the Response to Exercise—*

The arteriovenous oxygen differences and the lactic acid in the leg before and after exercise, grouped according to the type of heart disease, behaved in practically the same manner in the different etiologic types. In certain groups the results are based on too few cases to be of definite significance, but they suggest that the etiology of the heart disease plays

TABLE 2—*The Effect of Standing on the Arteriovenous Oxygen Difference and the Lactic Acid of Five Normal Subjects and Six Patients with Congestive Failure\**

Diagnosis and Number of Cases	Arteriovenous Oxygen Difference, Vol per Cent				Lactic Acid, Mg per 100 Cc			
	Leg		Arm		Leg		Arm	
	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes	During Rest	After Standing 2 Minutes
Control (5)	28.88 53	81.11.4 97	26.79 55	28.10.1 75	10.816.4 12.7	11.317.4 14.3	9.813.0 11.3	10.313.4 13.3
Congestive failure (6)	62.99 81	82.15.8 11.2	31.10.5 65	58.12.8 91	11.518.4 14.3	12.020.6 15.3	10.618.8 13.2	12.620.6 15.4

\* The averages appear in bold faced type

little or no part in the nature of the peripheral circulatory response. The exception in our series was a patient with congenital heart disease and "dry" failure. This patient, a man aged 20, with a probable large intra-ventricular septal defect, showed an unusually high arteriovenous oxygen difference in his femoral blood during rest. This evidence of decreased blood flow was probably due to the intracardiac shunting of blood from the left to the right side and a consequent decrease in the output of blood through the aorta into the peripheral circulation. This patient also showed the highest value for lactic acid in his femoral venous blood after exercise.

*Relationship of Edema to the Flow of Blood Through the Legs—*

Harrison and Pilcher<sup>9</sup> reported that in the absence of acidosis or intoxication due to digitalis the flow of blood through the edematous extremi-

<sup>9</sup> Harrison, T. R., and Pilcher, C. Studies in Congestive Heart Failure I. The Effect of Edema on Oxygen Utilization, *J. Clin. Investigation* 8:259 (Feb.) 1930.

ties, as measured by the arteriovenous oxygen difference, is increased. Our results did not confirm this. In the one patient with compensated and later with decompensated circulation and with moderate edema of the legs the arteriovenous oxygen difference in the legs during rest rose from 3.1 to 5.8 per cent. The patient, suffering from hypertensive heart disease, showed no evidence of acidosis or of intoxication due to digitalis. The data recorded in table 3 indicate a lack of relationship between the degree of edema and the arteriovenous oxygen difference. Moreover, when the average femoral arteriovenous oxygen differences of the patients showing edema of the legs (table 3) are compared with the

TABLE 3—*The Relationship Between the Degree of Peripheral Edema and the Arteriovenous Oxygen Difference and Lactic Acid in Seventeen Patients with Congestive Failure*

Case	Degree of Edema	Arteriovenous Difference During Rest, Vol per Cent		Lactic Acid During Rest, Mg per 100 Cc Leg
		Leg	Arm	
1	0	6.0	2.7	13
2	0	9.0	3.1	13
3	0	8.0	8.4	11
4	0	11.0	13.2	15
5	+	8.4	3.1	14
6	+	9.2	10.3	12
7	+	6.0	9.9	10
8	+	5.0	7.5	12
9	+	5.7	5.8	
10	++	5.8	2.7	19
11	++	8.2	10.5	11
12	++	3.4	6.3	15
13	+++	12.9	11.6	11
14	+++	6.8	5.8	
15	++++	8.0	7.7	18
16	++++	7.1	9.4	13
17	++++	9.9	8.0	16
Average for normal persons		4.7	4.7	13
Average for patients with compensated heart disease		3.6	5.1	12
Average for patients with "dry" failure		6.1	6.2	13
Average for patients with congestive failure		7.8	7.5	14

average values for normal persons, for patients with compensated cardiac disease and for patients with "dry" failure, it is evident that the values in the presence of edema are greater than in any of the other groups. These values, also, are nearly the same as the average values for the arteriovenous oxygen difference in the arm in the same group. This agreement between oxygen differences in the arm and in the leg is similar to that found in the group without edema and is substantial evidence that an increased blood flow in the leg does not exist.

*Relationship Between the Lactic Acid and the Oxygen Content of the Venous Blood of the Leg*—The question arose as to whether the high lactic acid values which were obtained could be related to the slow blood flow, causing either anoxemia of the tissues or a deficient removal

of lactic acid from the part where it was formed. This problem cannot be answered with certainty. Some evidence on this point may be gained by comparison of the oxygen content of the femoral venous blood immediately after exercise in patients showing a low lactic acid value (below 25 mg per hundred cubic centimeters) and in those with high lactic acid (above 35 mg). Although the patients with the most marked evidence of anoxemia, i. e., oxygen values of 2 volumes per cent or less, showed relatively high lactic acid volume, there were many patients with a high oxygen content and evidence of rapid blood flow who also showed high lactic acid values.

## COMMENT

Economic functioning of the circulation depends on the supply to the tissues of an amount of oxygen adequate for the degree of activity of the cells. During work the increased demand for oxygen by a large mass of tissue, such as the lower extremity, is met through a number of functions: an increased cardiac output, a widening of the arteriolar and capillary bed, with a resultant higher capillary blood pressure gradient, an increased degree of utilization of oxygen, and probably also an alteration in the oxidation capacity within the cells. If one or more of these factors become insufficient, the balance of the protoplasmic dynamics may become temporarily or permanently disturbed, as manifested particularly by changes in the chemical metabolism. Thus the efficiency of the circulation does not depend solely on the capacity of the heart to increase its pumping function. In normal persons the greatest efficiency of the cardiovascular system is often attained by a good peripheral utilization of oxygen with a relatively slight increase in the work of the heart. The degree of loss of oxygen from the arterial blood in relation to the oxygen consumption of the tissues is therefore one of the best measures of the state of the peripheral circulation.

It has been claimed that the capacity of muscle tissue to resynthesize and oxidize lactic acid in situ is dependent on the effectiveness of the local circulation. Hence the peripheral utilization of oxygen and the escape of lactic acid into the venous blood are supposedly closely related. Determination of the relationship between lactic acid and muscular work in patients with cardiac disease is particularly difficult, because there is no definite agreement regarding this interrelation in health. The rôle of the formation of lactic acid in the contraction of amphibian and mammalian muscle was first demonstrated by Fletcher and Hopkins<sup>10</sup> and was further studied by others, mainly by the school of Meyerhof.<sup>11</sup> Hill, Long and Lupton<sup>41</sup> found that the blood lactic acid after the subject

10 Fletcher, W. M., and Hopkins, F. G. Lactic Acid in Amphibian Muscle, *J. Physiol.* **35** 247, 1906-1907.

11 Meyerhof, O. Zur Verbrennung der Milchsäure in der Erholungsperiode des Muskels, *Arch. f. d. ges. Physiol.* **175** 88, 1919.

had walked at a rate of  $3\frac{1}{2}$  miles (5.6 kilometers) per hour for twenty-eight minutes rose from 20.9 to 36.6 mg. Walking at the rate of  $4\frac{1}{10}$  miles (6.6 kilometers) per hour for thirty-three minutes induced a change of from 21.4 to 58.9 mg. In a later study Long<sup>12</sup> observed similar changes. Owles,<sup>13</sup> on the other hand, failed to observe changes in the blood from the veins of the arm in two trained subjects following a walk of thirty minutes at  $4\frac{1}{2}$  miles (7.2 kilometers) per hour. More recently, Cook and Hurst<sup>14</sup> investigated the lactic acid in man during rest and during exercise. In two subjects accustomed to walking long distances they observed no change in the lactic acid content of the blood following walking at 4 miles (6.4 kilometers) and at  $4\frac{1}{2}$  miles, respectively, per hour for thirty minutes. In two other subjects not accustomed to strenuous walking, a somewhat shorter walk was followed by a doubling of the blood lactic acid in the arm and femoral vein. In contrast to our experience, however, the rises in the femoral blood and in that of the arm were practically identical. The explanation of this apparent discrepancy may be the difference in the duration of the exercise, that is, following the longer exercise a complete mixing of the lactic acid throughout the blood occurred, so that the contents were in equilibrium. Cook and Hurst also emphasized that the threshold of exercise beyond which an increase of lactic acid appears in the blood depends on the fitness or training of the individual. There is little doubt that the discrepancies in the various findings are due partly to differences in methods of approach to the problem as well as to the delicacy of the method of lactic acid determination.

Eppinger, Kisch and Schwarz<sup>2</sup> presented evidence indicating that the resynthesis of lactic acid is one of the first disturbances in heart failure. The increased circulation of lactic acid in the blood is supposed to cause acidosis, which decreases the buffering capacity of the blood. These chemical alterations then place an increased burden on the heart, leading to failure. Eppinger and his associates did not study directly the utilization of oxygen by the working muscles or the overflow of lactic acid into the blood. Their method of approach was indirect, through a study of the respiratory function of the entire body. A few observations by Diaz and Cuenca<sup>15</sup> on the lactic acid content of the venous

12 Long, C. N. H. Muscular Exercise, Lactic Acid, and the Supply and Utilisation of Oxygen. XIV The Relation in Man Between the Oxygen Intake During Exercise and the Lactic Acid Content of the Muscles, *Proc. Roy. Soc., London*, s. B. **99**, 167, 1925-1926.

13 Owles, W. H. Alterations in the Lactic Acid Content of the Blood as a Result of Light Exercise, and Associated Changes in the CO<sub>2</sub>-Combining Power of the Blood and in the Alveolar CO<sub>2</sub> Pressure, *J. Physiol.* **69**, 214, 1930.

14 Cook, L. C., and Hurst, R. H. Blood Lactic Acid in Man During Rest, *J. Physiol.* **79**, 443, 1933.

15 Diaz, C. J., and Cuenca, B. S. Etudes cliniques sur l'utilisation de l'acide lactique, *Ann. de méd.* **28**, 501, 1930.



blood at rest and following exercise may be looked on as a confirmation of Eppinger's contention. Hefter and Okunew<sup>16</sup> claimed that in the presence of rheumatic fever with cardiac decompensation and in a state of decompensation, regardless of its etiology, there is a decreased capacity of the muscles to utilize oxygen, and that the resynthesis of the lactic acid is disturbed.

In normal subjects we found that the oxygen utilization in the arm and that in the leg were approximately the same. When the patient stood for two minutes there was a considerably greater peripheral utilization both in the arm and in the leg, particularly in the leg. This increased utilization cannot be explained by an equivalent increase in the metabolism with an unchanged blood flow, for it was also present in the passive arm, which had an essentially unaltered metabolism. The change reflects a decreased blood flow through the extremities during standing, as was suggested by Florkin, Edwards and Dill.<sup>17</sup>

Immediately following exercise the average oxygen utilization more than doubled and then promptly (within ten minutes) returned to normal. The increased utilization of oxygen in the leg was undoubtedly due to the fact that the increased metabolism of the working muscles caused a demand for oxygen which was relatively greater than the increase in the blood flow to these muscles. It was particularly surprising, however, to find that the oxygen utilization in the resting arm had increased to practically the same degree as that in the exercising leg. This markedly increased oxygen utilization of the arm may be explained by a passively decreased blood supply to the arm, as a result of an increased blood flow in the leg, or by a local vascular constriction in the arm which retarded the blood flow. Such local reflex retardation of the blood flow in the resting tissues, when other tissues are active, has recently been demonstrated in animals by Rein.<sup>18</sup> It is this reflex regulation of the circulation which enables the working tissues to obtain a better blood supply. According to Bainbridge,<sup>19</sup> the oxygen supply to muscles during strenuous exercise may increase from ten to fifteen times. That the cardiac output cannot increase correspondingly is obvious, for it would necessitate an output of from 40 to 60 liters per minute, which with a heart rate of from 120 to 140 would yield a stroke volume of from 300 to 400 cc—a physical impossibility. The regional constriction of the vascular areas during rest, however, not only results

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16 Hefter, A. I., and Okunew, D. F. Ueber Veränderungen des peripheren Stoffwechsels im Zusammenhang mit den Blutkreislaufstörungen bei der Muskelarbeit, *Ztschr. f. d. ges. exper. Med.* **79** 806, 1931.

17 Florkin, M., Edwards, H. T., and Dill, D. B. Oxygen Utilization in the Legs of Normal Men. I. Effect of Posture, *Am. J. Physiol.* **94** 459, 1930.

18 Rein, H. Vasomotorische Regulationen, *Ergebn. d. Physiol.* **32** 28, 1931.

19 Bainbridge, F. A. *The Physiology of Muscular Exercise*, ed. 3, New York, Longmans, Green & Co., 1931.

in a decreased flow of blood through these areas during rest but may be a factor in the elevation of the arterial blood pressure observed during exercise. The elevated arterial pressure makes the increased shunting of blood into the dilated vascular regions of the working areas particularly effective, because it makes possible a considerably increased regional blood flow without an increase in cardiac work.

The increase in the lactic acid in the femoral venous blood after exercise was, of course, due to the fact that the acid was formed in the active muscle faster than it could be either resynthesized *in situ* or conveyed away by the blood stream to undergo reconversion into glycogen or oxidation in the liver or elsewhere.

It is significant that the immediate change in the lactic acid of the blood of the arm was slight. Ten minutes later, however, the level was similar in the arm and in the leg. These observations definitely indicate that moderate muscular exercise which is carried out by the subjects with ease is followed by a considerable output of lactic acid into the blood. As a result of the mixing effect, an equalization of the lactic acid level throughout the circulation occurs within ten minutes.

In patients with heart disease and with moderate impairment of cardiac reserve, but with no evidence of failure, who with two exceptions performed the exercise without dyspnea the behavior of the peripheral circulation was similar to that in the control group. The only striking difference was the higher basal heart rate, with a greater increase and a slower return to the level present during rest. The same work was performed, therefore, with a greater expenditure of cardiac energy.

The group with obvious evidence of failure of the circulation without peripheral engorgement included patients with cardiac lesions of varied etiology. The degree of functional impairment varied from moderate to severe, but in no case was it so severe as in the group with congestive failure. The venous pressures were within normal limits, but the vital capacity was appreciably reduced. This group also showed essentially the same oxygen utilization and lactic acid level during rest as did the control group, following exercise, however, there were a somewhat greater peripheral utilization of oxygen and a somewhat greater output of lactic acid. The differences statistically are not conclusive. Patients in this group also exhibited a marked rise and a slow return of the heart rate following exercise. It was significant that several patients who were barely able to perform the moderate exercise because of intense dyspnea showed normal oxygen utilization and lactic acid output. This group of patients clearly demonstrates that the source of disability does not lie in the inadequacy of the peripheral circulation. We have presented elsewhere<sup>3b</sup> evidence of disturbance of the pulmonary circuit in this type of patient.

The patients with congestive failure were completely disabled. The vital capacities of the lungs were conspicuously low, the venous pressures,

rather high. Their peripheral oxygen utilization was higher than normal, both during rest and following exercise. The lactic acid outputs were also greater than in the control group. It is particularly significant that the average level of the lactic acid during rest was essentially the same as in the control group. Our results, therefore, do not indicate a relationship between the degree of circulatory insufficiency and the level of the lactic acid during rest. As some of the patients showed a high oxygen utilization and a slow blood flow, it follows that the lactic acid during rest may not be appreciably influenced by a slow blood flow. The same lack of correlation between the degree of blood flow and the level of lactic acid in individual cases was observed after exercise.

The finding of high oxygen utilization at rest indicates a decreased cardiac output in these patients. Moreover, the fact that this utilization increased after exercise to such an extent that there was in several

TABLE 4—*The Lactic Acid During Rest in Eleven Patients with Hepatic Disease*

Patient	Lactic Acid During Rest, Mg per 100 Cc	Diagnosis
G O'M	11	Catarrhal jaundice
W A	15	Catarrhal jaundice
W C	13	Arsphenamine hepatitis
H M	18	Arsphenamine hepatitis
S K	25	Jaundice? carcinoma of the liver
M L	14	Cirrhosis of the liver
W B	16	Cirrhosis of the liver
T R	18	Cirrhosis of the liver, arteriosclerotic heart disease
R K	21	Cirrhosis and acute hepatitis
J L	27	Toxic hepatitis
M G	18	Acute yellow atrophy

instances an unusually low oxygen content of the femoral venous blood suggests that the rise in output after exercise was insufficient and frequently inadequately compensated by the increase in the peripheral utilization of oxygen.

Our experience, therefore, does not agree entirely with the observations of Meakins and Long,<sup>20</sup> who observed, even during rest, an increased concentration of the blood lactic acid in patients with severe circulatory failure and who considered that the amount of lactic acid in the blood is in proportion to the severity of the circulatory failure. There is a possibility, however, that in patients with cardiac disease who are moribund or who have severe hepatic damage the lactic acid level is elevated, but we have not studied this aspect of the problem. In some patients with normal cardiovascular systems and with hepatic damage alone we have observed an elevated lactic acid content of the blood (table 4). Although the lactic acid level of the blood in patients with cirrhosis of the liver may be high, the response to exercise of two subjects was of essentially the same character as in normal subjects.

20 Meakins, J, and Long, C N H. Oxygen Consumption, Oxygen Debt and Lactic Acid in Circulatory Failure, *J Clin Investigation* 4 273, 1927

## COMMENT

As a result of these studies, therefore, we consider that there is no evidence of a primary disturbance of the peripheral circulation as the precipitating factor in heart failure. There is evidence, however, that the peripheral circulation does not play a purely passive rôle, as was once widely believed. In normal persons, the cardiovascular functions can be increased efficiently and a certain amount of the load removed from the heart itself by peripheral vascular reflexes which tend to shunt blood where it is most needed and under greater pressure, particularly by increased oxygen utilization. The same factors, to a greater degree, tend to operate in patients with heart disease, with and without evidence of failure. With the aid of the peripheral circulation, compensation for an inadequate cardiac function may be achieved. Indeed, failure of the peripheral circulation as measured by an inadequate supply of oxygen to the tissues is usually a late manifestation of what is commonly thought of as "congestive heart failure." Frequently it never occurs, for long before it becomes a significant factor in the clinical picture, gross disturbances of the pulmonary circulation as a result of the failing heart incapacitate the patient or lead to his death.

## SUMMARY AND CONCLUSIONS

1 The utilization of oxygen and the production of lactic acid in the upper and lower extremities were compared in normal subjects and in patients having heart disease with and without congestive failure.

2 During rest, the average oxygen utilization was essentially the same in the arm and in the leg. In heart disease without congestive failure the utilization of oxygen during rest was normal in magnitude, but with congestive failure there was a tendency toward an increased peripheral utilization. This is evidence that in congestive failure the blood flow through the extremities is frequently reduced. Edema of the leg was not found to be associated with a relatively or absolutely increased local blood flow.

3 On standing, the oxygen utilization of the extremities increased both in subjects with normal and in those with diseased cardiovascular systems, as a result, in part at least, of decreased blood flow.

4 Immediately after exercise the oxygen utilization increased markedly, but it returned to the level during rest within ten minutes. In a patient with heart disease the oxygen content of the femoral venous blood immediately after exercise was as low as 11 volumes per cent.

5 The average resting level of the lactic acid in the extremities was between 12 and 14 mg. for all groups. Immediately after the patients ceased walking, the lactic acid of the femoral venous blood draining the active muscle more than doubled, it then fell rapidly during the next

ten minutes but did not reach the level observed during rest within twenty minutes. The lactic acid content of the venous blood of the inactive arm rose slightly immediately after the exercise, but in ten minutes was similar to that of the leg, as a result of the mixing effect of the circulation. With the increasing severity of circulatory failure there was a tendency for the femoral lactic acid to rise to a higher level than normal immediately after exercise and to fall more slowly.

6 With the exception of one case of congenital intraventricular septal defect, the etiology of the heart disease played no rôle in the nature of the peripheral circulatory response.

7 Certain patients showed marked cardiac disability, i. e., orthopnea, dyspnea and low vital capacity of the lungs, and yet they had normal venous pressure, no edema or hepatic enlargement and normal oxygen utilization and lactic acid response. The disability in these patients cannot be explained on the basis of the behavior of the peripheral circulation. When disturbances in the lactic acid production and peripheral circulation occur, they are the result, and not the cause, of heart failure.

This investigation was conducted with the technical assistance of Miss Dwight Baker and Miss Rose Shore.

# Progress in Internal Medicine

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## LIVER AND BILIARY TRACT

REVIEW OF THE LITERATURE OF 1933 AND 1934

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Mann,<sup>1</sup> in a review entitled "The Functions of the Gall Bladder," published in 1924 a bibliography of 95 articles. Ivy,<sup>2</sup> in a similar review in 1934, published a bibliography of 553 articles, the majority of which represented work done during the intervening decade. The contrast between these two reviews illustrates dramatically both the widespread interest in this field of medicine and the voluminous nature of the resultant literature. This is true not only of the physiology of the gallbladder but of that of the liver and the rest of the biliary tract. Under these conditions it seemed best in reviewing the literature for 1933 and 1934 to outline, so far as possible, the more important trends of investigation by citing significant papers rather than to attempt reference to the entire literature for these years.

### PHYSIOLOGY OF THE GALLBLADDER

Ivy,<sup>2</sup> in reviewing the physiology of the gallbladder, pointed out that during the past decade no really new activities or functions have been discovered which had not been suggested before but that it is now believed that the physiology of the gallbladder resembles in principle the general activities of the intestine, namely, absorption, secretion and motor activity.<sup>3</sup>

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1 Mann, F. C. The Functions of the Gall Bladder, *Physiol Rev* **4** 251 (April) 1924

2 Ivy, A. C. The Physiology of the Gall Bladder, *Physiol Rev* **14** 1 (Jan) 1934

3 Harding, H. E. Functions of the Epithelium of the Gallbladder, *Guy's Hosp Rep* **84** 186 (April) 1934

The gallbladder is one of the mechanisms concerned in the correlation of the secretory activity of the liver and the digestive activity of the other portions of the gastro-intestinal tract. According to the classic concept, this viscus stores and concentrates much of the bile secreted by the liver during the interdigestive period in order to supply this store of concentrated bile at the beginning of the next digestive period and so to aid in the digestion and absorption of fatty foods in particular. This functional activity is made possible by the coordinated action of the three types of primary activity to which reference has been made.

The normal gallbladder concentrates the hepatic bile that enters it to a density from four to ten times that of the original. This is accomplished primarily by the absorption of water and inorganic salts so that the bile tends to come into osmotic equilibrium with the blood serum. In this process of concentration the bile is slightly acidified. The other biliary constituents appear to be absorbed only slightly, if at all, by the normal gallbladder, though there are many questions with regard to details which remain to be decided.

It is probable that under normal conditions the gallbladder proper forms only a small quantity of mucoid secretion. In conditions of acute irritation it ceases to concentrate hepatic bile and instead pours out a fluid which may vary widely from the normal bile in its composition. Because of the change in the concentrating power of the gallbladder the composition of the bile, as emphasized by Ravdin and his associates,<sup>4</sup> may show great variations in disease.

The gallbladder manifests two types of motor activity. One type may be called a tonic contraction. It produces a sustained rise in pressure which persists from five to thirty minutes or more. The other type may be called a tonus rhythm and is manifested by rhythmic contraction and relaxation occurring at a rate of from 2 to 6 times a minute. In each type the muscular coat may contract either as a whole or in part. In some species there may be a peristalsis-like type of motor activity during evacuation.

While formerly there was controversy as to whether the gallbladder ever empties, this can now be accepted as a fact. Once it is agreed that the gallbladder does become evacuated, consideration of the mechanism involved becomes paramount. The usually accepted view is that evacuation is the result of muscular contraction, though some investigators, as Mairrazzi,<sup>5</sup> still deny such activity. Ivy<sup>6</sup> and his students

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4 Ravdin, I. S., Riegel, C., Johnston, C. G., and Morrison, P. J. Studies in Biliary Tract Disease, *J. A. M. A.* **103** 1504 (Nov. 17) 1934.

5 Mairrazzi, A. S. Emptying of Gallbladder, *Am. J. Physiol.* **102** 293 (Nov.) 1932.

6 Ivy, A. C. Factors Concerned in the Evacuation of the Gall Bladder, *Medicine* **11** 345 (Sept.) 1932.

demonstrated that the presence of acid or of fatty substances in the duodenum and upper portion of the intestine causes the formation of a hormone (cholecystokinin) which stimulates contraction of the gallbladder. Ivy expressed the belief that the contraction and evacuation of the gallbladder are due primarily to the stimulus of this hormone.

The efficiency of such fatty substances as cream, egg yolk, olive oil and oleic acid in producing contraction and emptying of the gallbladder is to be explained rather by their action in stimulating the production of cholecystokinin in the mucosa of the duodenum than by a specific stimulatory effect of these materials either on nerve endings in the duodenum before, or on the wall of the gallbladder after, absorption. Ivy also showed the effectiveness of cholecystokinin in causing emptying of the gallbladder in man.

The importance of the sphincteric mechanism at the duodenal end of the common duct, as pointed out by Giordano and Mann,<sup>7</sup> must not be minimized. Ivy, Voegtlin and Greengard<sup>8</sup> recently reported experiments on a human subject in whom, after the injection of a solution of cholecystokinin, pain in the gallbladder was produced by the contraction of the gallbladder concurrently with the development of spastic obstruction in the intramural portion of the common bile duct. In this case intraduodenal administration of magnesium sulphate was effective in relieving the spasm and distress. Since cholecystokinin is formed after the eating of fats, functional disturbances analogous to those reported by Ivy, Voegtlin and Greengard may explain some of the intolerance of fats which is a frequent complaint of patients with chronic cholecystitis. In addition to this humoral mechanism, the gallbladder is under the control of the nervous system and possesses sensory and motor innervation. The efferent fibers from the vagus nerve are predominantly motor in character, those from the splanchnic nerves, inhibitory. The motor activity of the duodenal musculature and the sphincter of Oddi likewise are subject to nervous regulation, and the view of a reciprocal relationship between the emptying of the gallbladder and the relaxation of the sphincter is generally accepted though many of the details regarding the exact mechanism involved are still unexplained.

Ivy described the evacuation of the gallbladder after a meal of egg yolk and cream as due primarily to a more or less sustained tonic contracture of the musculature. The contraction is excited in part by a

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<sup>7</sup> Giordano, A. S., and Mann, F. C. The Sphincter of the Choledochus, *Arch. Path.* **4** 943 (Dec.) 1927.

<sup>8</sup> Ivy, A. C., Voegtlin, W. L., and Greengard, H. The Physiology of the Common Bile Duct. A Singular Observation, *J. A. M. A.* **100** 1319 (April 29) 1933.



hormone (cholecystokinin) and in part by a reflex nervous mechanism. The sphincter of Oddi and the duodenal musculature relax and permit bile to be expelled by the contracting gallbladder. Duodenal peristalsis may exert a milking action on the intramural portion of the common duct which assists but is not essential to evacuation. Following evacuation which may be but usually is not complete, the common duct is closed by the choledochoduodenal barrier, and the gallbladder relaxes as hepatic bile again enters the reservoir.

When one considers the several mechanisms and the precise integration of their action which is necessary for the normal functioning of the gallbladder and biliary tract and the variety of influences which may affect one or the other of the mechanisms, the existence of functional disorders of motility, the so-called biliary dyskinesia, is not surprising. An extensive literature on this topic has developed in Germany during the past decade which Ivy and Sandblom<sup>9</sup> have recently reviewed. Biliary dyskinesia is an important clinical problem, and its solution will serve to explain many otherwise obscure clinical observations. It deserves much more widespread clinical recognition and study than it receives at the present time. For instance, it is a common observation during duodenal drainage to find that no concentrated bile is obtained after stimulation with magnesium sulphate but that a free flow follows the instillation of egg yolk or olive oil. Does such an observation indicate that in that patient reflex stimulation was insufficient to cause evacuation of the gallbladder, which did, however, respond to hormonal stimulation? Can this method be used to study the relative influence of the two mechanisms in an individual patient?

#### DIAGNOSIS AND TREATMENT OF CHRONIC CHOLECYSTITIS

Numerous authors, among them Twiss and Greene<sup>10</sup>, Lyon<sup>11</sup>, Dreier, Crellin and Rehfuess<sup>12</sup>, Brown,<sup>13</sup> and Ivy and Bergh<sup>14</sup> presented brief reviews of the physiology of the gallbladder and pointed

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9 Ivy, A. C., and Sandblom, P. Biliary Dyskinesia, *Ann Int Med* 8 115 (Aug.) 1934

10 Twiss, J. R., and Greene, C. H. Dietary and Medical Management of Diseases of the Gall Bladder. Newer Points of View, *J. A. M. A.* 101 1841 (Dec. 9) 1933

11 Lyon, B. B. V. Diagnosis and Management of Gall Tract, Particularly Gall Bladder Disease, *Am. J. Digest. Dis. & Nutrition* 1 18 (March) 1934

12 Dreier, J. F., Crellin, W. N., and Rehfuess, M. E. The Physiology of the Gall Bladder, *Rev. Gastroenterol.* 1 24 (March) 1934

13 Brown, T. R. The Results of Treatment—Medical and Surgical—in Gall Bladder Disease from a Clinician's Viewpoint *Am. J. Digest. Dis. & Nutrition* 1 221 (June) 1934

14 Ivy, A. C., and Bergh, G. S. The Applied Physiology of the Extra-Hepatic Biliary Tract, *J. A. M. A.* 103 1500 (Nov. 17) 1934

out the application of the newer points of view to improvement of the diagnosis and therapeutic management of the patient with disease of the liver or biliary tract. They emphasized that the three most important elements in the diagnosis of cholecystic disease are (1) the history of the case, (2) cholecystography and (3) nonsurgical drainage of the biliary tract.

The history remains of paramount importance in diagnosis. Brown in particular emphasized the value of a carefully taken, thorough and well studied history, comprising not only the record of the digestion but the entire history of the patient. By this means and a careful physical examination, he was able to make the correct diagnosis in slightly less than 85 per cent of the cases which he reported.

*Cholecystography*—The value of the cholecystogram in the diagnosis of disease of the gallbladder is universally accepted. An attempt to evaluate the reliability of the method by statistical analysis is difficult because of the various factors which enter into the selection of the patients on whom this procedure is performed. Ferguson and Palmer,<sup>15</sup> who reported a study of 2,070 cases, concluded that good visualization of the gallbladder and no evidence of stones indicated the diagnosis of a normal gallbladder with an accuracy of probably over 98 per cent. The accuracy of diagnosis when stones were visualized, either as positive or negative shadows, likewise approached 100 per cent. When visualization of the gallbladder failed and there was a clinical history of cholecystitis, the diagnosis was later proved to be correct in 90 per cent of the cases. If the clinical history was lacking, the diagnostic accuracy was less than 66.6 per cent. The authors found that in the cases in which cholecystic disease was demonstrated at operation a history of colic was noted almost as frequently as cholecystographic evidence of the lesion. Ferguson and Palmer used the intravenous method of administering the dye. Buisson<sup>16</sup> and Hess<sup>17</sup> likewise stressed the value of the intravenous method in obtaining the cholecystogram.

Kirklin<sup>18</sup> pointed out that when the oral method is properly executed its efficiency is equal to that of the intravenous method. In a series of 732 cases in which the diagnosis was established at operation, he

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15 Ferguson, A. N., and Palmer, W. L. Cholecystography. Its Clinical Evaluation. A Study of Two Thousand and Seventy Cases, *J. A. M. A.* **100** 809 (March 8) 1933.

16 Buisson, P. Interpretation of Negative Cholecystogram, *Presse med.* **41** 1386 (Sept. 6) 1933.

17 Hess, L. R. X-ray in Diagnosis of Gallbladder Disease, *Canad. M. A. J.* **29** 396 (Oct.) 1933.

18 Kirklin, B. R. Persisting Errors in the Technic of Oral Cholecystography. A Procedure Designed to Avoid Them, *I. A. M. A.* **101** 2103 (Dec. 30) 1933.

found the accuracy of the cholecystogram in revealing a normal gallbladder was 89.5 per cent. Gallstones were detected in 70.8 per cent of the cases, but evidence of cholecystic disease was present in 99 per cent. Of the patients showing changes in the cholecystogram, 98.6 per cent had cholecystic disease. Foged<sup>19</sup> also reported similar results with the oral administration of the contrast substance.

The feeding of carbohydrate results in the secretion of concentrated bile by the liver and at the same time favors storage of that bile in the gallbladder. Antonucci,<sup>20</sup> in particular, pointed out that the intravenous injection of 125 cc of a 40 per cent solution of dextrose followed by the intravenous injection of 3 Gm of tetiothalein sodium produced rapid elimination of the dye and distention of the gallbladder so that maximum opacity of the dye in the gallbladder was obtained in two hours. Liverani,<sup>21</sup> Zappala,<sup>22</sup> and others confirmed the advantages of this technic. Stewart and Illick<sup>23</sup> used the same principle in improving the technic of cholecystography by the oral method. The patient is given several cups of tea with extra sugar in the afternoon. The regular evening meal is allowed at 6 p. m., and the first dose of tetiothalein sodium is given at 7 p. m. Tea with sugar is given later in the evening. The following morning no breakfast is allowed, and cholecystograms are taken twelve and sixteen hours after the first dose of the dye. The noon meal consists of fruit juice, jello, fruit salad and tea, and it is followed by another dose of the dye. Tea is again given in the afternoon, and an evening meal similar to the luncheon is allowed. A third dose of dye is given in the evening. A thirty-six hour examination is made the next morning. The films normally exhibit marked concentration of opaque bile in the gallbladder. A study is then made after a fatty meal to determine how well and rapidly the gallbladder empties. When carried out successfully, such methods promise to increase even further the precision of the cholecystographic methods of diagnosis.

*Nonsurgical Drainage of the Biliary Tract*—The diagnostic value of nonsurgical drainage of the biliary tract is a matter concerning which there is the widest divergence of opinion. When the new type

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19 Foged, J. Cholecystography, *Acta chir Scandinav* **75** 1105 (June 8) 1934

20 Antonucci, C. Rapid Cholecystography, *Presse med* **40** 983 (June 22) 1932

21 Liverani, E. Biochemical and Experimental Research in Rapid Cholecystography of Antonucci and Modification of Method, *Policlinico (sez med)* **40** 128 (Feb.) 1933

22 Zappala, G. Cholecystography According to Antonucci's Method, *Policlinico (sez chir)* **40** 541 (Sept 15) 1933

23 Stewart, W. H., and Illick, H. E. Intensified Oral Cholecystography Preliminary Report, *Am J Digest Dis & Nutrition* **1** 337 (July) 1934

of tip with a terminal weight and the simplified technic described by Twiss<sup>24</sup> are used, it is not a formidable procedure and can be used as a routine to aid in the diagnosis. In our experience<sup>25</sup> the presence or absence of concentrated bile, especially if this can be confirmed by chemical methods, and the conditions under which the concentrated bile is obtained give evidence regarding both the concentrating power and the motor activity of the gallbladder. As such, the findings afford a valuable confirmation of those obtained by cholecystography. The finding of crystals of cholesterol or of calcium bilirubinate in quantity, as Rousselot and Bauman<sup>26</sup> agreed, is strong presumptive evidence of the presence of biliary calculi.

Cultures obtained from the bile and the demonstration of the presence of *Bacillus typhosus*, as pointed out by Bigelow and Anderson<sup>27</sup> and by Senftner and Coughlin,<sup>28</sup> are essential in the recognition of typhoid carriers, especially if cholecystectomy is to be done for the cure of the carrier state.

*Treatment*—The factors of stasis, metabolic disturbance and infection are generally accepted as of prime importance in the production of cholecystitis or cholelithiasis. While the clinician may make a diagnosis of cholecystitis, it is now generally accepted that the pathologic process is not limited to the gallbladder but that the entire biliary tract is affected to a greater or less extent. The problem of the physician is not the cure of an acute condition but the management of a chronic disease. Treatment is aimed at the relief or correction of the elements of stasis, metabolic disturbance and infection. As already pointed out, these conditions may result from a variety of causes, and the details of the method of treatment may vary with the individual patient. Under these conditions surgical drainage or removal is but one factor, though often a major one, in the management of disease of the biliary tract. Surgical intervention is indicated in the presence of

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24 Twiss, J. R. A New Type of Duodenal Tube Tip, *Am J M Sc* **185** 109 (Jan) 1933, Technic of Nonsurgical Drainage of the Biliary Tract, *J A M A* **100** 792 (March 18) 1933.

25 Carter, R. F., Greene, C. H., and Twiss, J. R. Diagnosis and Treatment of Diseases of the Liver and Biliary Tract, New York, New York Post-Graduate Medical School, 1934.

26 Rousselot, L. M., and Bauman, L. Cholesterol Crystals and "Calcium Bilirubinate Granules" Their Significance in Bile Obtained Through the Duodenal Tube, *J A M A* **100** 254 (Jan 28) 1933.

27 Bigelow, G. H., and Anderson, G. W. Cure of Typhoid Carriers, *J A M A* **101** 348 (July 29) 1933.

28 Senftner, H. F., and Coughlin, F. E. Typhoid Carriers in New York State with Special Reference to Gall Bladder Operations, *Am J Hyg* **17** 711 (May) 1933.

gallstones and in a few cases with characteristic history and symptomatology. Graham and Mackey<sup>29</sup> pointed out that in the absence of severe pain or typical biliary colic the results of cholecystectomy in cases of stoneless gallbladder are likely to be unsatisfactory in approximately 40 per cent of the patients. Furthermore, they added that at present there seems to be little justification for operation in patients who have only the early beginnings of cholecystic disease, unless one is interested in the prevention of complications. Brown<sup>13</sup> and Howard,<sup>30</sup> in reporting a series of 84 cases observed for from two to fifteen years, stated that in only 59 per cent did the patient have complete or relative cure following operation.

The importance of careful follow-up in either medical or surgical cases is shown by the report of Blackford, King and Sherwood.<sup>31</sup> They studied 200 patients with chronic cholecystitis who had been treated medically for from five to fifteen years. Thirty-seven per cent of the patients had satisfactory relief for an average period of more than eight years without operation. Forty-eight per cent either came to operation later because of continuation of symptoms or should have been operated on for that reason. Fifteen per cent of the patients died, but in only 1 per cent was death due directly to disease of the gallbladder.

#### JAUNDICE

During the two years under consideration there has been no change in the views generally held regarding the pathogenesis of jaundice. Mann and Bollman,<sup>32</sup> who summarized much of the experimental investigation, pointed out that complete removal of the liver produces jaundice which may be considered as entirely hemolytic in origin. In this condition the bilirubin of the serum is increased and gives only the indirect reaction to the van den Bergh test. In other types of experimental jaundice produced by hepatic injury or by occlusion of the bile duct, the serum bilirubin is increased, and the van den Bergh reaction is direct. This observation affords complete agreement between the

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29 Graham, E. A., and Mackey, W. A. A Consideration of the Stoneless Gallbladder, *J. A. M. A.* **103** 1497 (Nov 17) 1934.

30 Howard, J. T. An Analysis of the Results of Biliary Tract Surgery, *Am. J. Digest. Dis. & Nutrition* **1** 270 (June) 1934.

31 Blackford, J. M., King, R. L., and Sherwood, K. K. Cholecystitis Study Based on Follow-Up After from Five to Fifteen Years of Two Hundred Patients Not Operated On, *J. A. M. A.* **101** 910 (Sept 16) 1933.

32 (a) Mann, F. C., and Bollman, J. L. Jaundice. A Review of Some Experimental Investigations, *J. A. M. A.* **104** 371 (Feb 2) 1935. (b) Bollman, J. L., and Mann, F. C. Liver and Bile, *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1934, vol. 3, p. 367.

experimental and the clinical types of hemolytic, hepatic and obstructive jaundice

Bollman and Mann<sup>32b</sup> further pointed out that in experimental obstructive jaundice the absence or alteration of bile from the intestine, the presence of biliary constituents in the blood and tissues and the associated functional impairment of the liver produce typical effects on the experimental animal. Nutritional disturbances and especially the decreased tolerance to meat are important. There is a tendency to the development of peptic ulcer. Anemia and a decrease in the proteins of the blood plasma are frequent, and ascites may be found. A reduction in the formation of bile salts is also a result of hepatic injury.

The clinical classification of jaundice requires no discussion at the present time. However, reference may be made to the studies of Snelling,<sup>33</sup> Altitzoglou<sup>34</sup> and Fuchs<sup>35</sup> on icterus neonatorum. They pointed out, as have other investigators, that during fetal life the liver is actively concerned in the formation of red blood cells and polycythemia is present. During the first two weeks of life the red cell count and the percentage of hemoglobin fall gradually. Excretion of bilirubin by the fetal liver is at a minimum, and during the first few days after birth there is a period of hepatic insufficiency until the excretion of bilirubin attains its normal degree of activity. The usual type of icterus neonatorum develops during this period. In addition to this benign type of icterus neonatorum, cases of icterus gravis are also seen in newborn infants. The majority of these cases are due either to infection or, in the familial type, to erythroblastosis.

The pathogenesis of "catarrhal" jaundice continues to be a source of controversy. It is accepted that while the majority of the cases of this condition are due to toxic or degenerative changes in the hepatic parenchyma, some may be due to infection of the smaller bile ducts or to capillary cholangitis, and in a few cases there may be true gastro-duodenal catarrh with obstruction of the common bile duct by a mucous plug. Hurst and Simpson<sup>36</sup> reviewed the literature dealing with the pathogenesis of this condition, they insisted that the various syndromes can be recognized clinically. In true catarrhal jaundice the cases occur sporadically in young persons. Jaundice is preceded by a period of anorexia, malaise, fever, nausea and gastro-intestinal disturbances. The liver is slightly enlarged and tender, and the gallbladder can frequently

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33 Snelling, C. E. Icterus Neonatorum, *J. Pediat.* **2** 399 (April) 1933

34 Altitzoglou, J. Blood Picture in Icterus Neonatorum Familiaris Gravis and Its Diagnostic Significance, *Monatschr. f. Kinderh.* **58** 329, 1933

35 Fuchs, H. Icterus Neonatorum Gravis with Especial Consideration of Infectious Type, *Schweiz. med. Wchnschr.* **63** 1129 (Nov. 4) 1933

36 Hurst, A. F., and Simpson, C. K. Catarrhal Jaundice and Mild Hepatic Necrosis. Their Pathology and Diagnosis, *Guy's Hosp. Rep.* **84** 173, 1934

be palpated. The levulose or galactose test of hepatic function gives negative results. In cases of primary parenchymal injury or necrosis, on the other hand, there may be a history of exposure to a toxic substance, such as arsphenamine or cinchophen, but otherwise the jaundice develops without prodromal symptoms. Following the appearance of jaundice, there develop anorexia, headache, weakness and tachycardia. This conception of Hurst is one of extreme interest. However, there are many cases of acute hepatic jaundice in which the clinical findings do not permit so distinct a differential diagnosis.

In many cases of jaundice, as pointed out by Flood, Seegal, Spock and Loeb,<sup>37</sup> even the differentiation of a hepatic from an obstructive type of icterus is difficult. It is in these cases in particular that the tests of hepatic function have been of greatest usefulness.

#### TESTS OF HEPATIC FUNCTION

*Carbohydrate Metabolism*—The rôle of the liver in carbohydrate metabolism is accepted, but the selection of the proper test to demonstrate changes in this activity of the liver is a cause of controversy. Althausen, Gunther, Lagen and Kerr<sup>38</sup> gave 20 units of insulin to a fasting patient, twenty minutes later 50 Gm of dextrose in 500 cc of water was administered orally, followed by a liter of water. By this means they thought they could obtain the simultaneous measurement of the glycogen reserve, the dextrose metabolism and the water-regulating function of the liver. Migneco<sup>39</sup> and Ricketts<sup>40</sup> tried this test on normal persons and on patients with hepatic disease. They found no essential difference between the behavior of the group of normal persons and that of patients with hepatic disease, and they did not consider the test a satisfactory measure of hepatic function.

The various factors which influence the tolerance to levulose were discussed in detail by Rowe, Plummer and McManus.<sup>41</sup> They empha-

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37 Flood, C. A., Seegal, D., Spock, B., and Loeb, R. F. Differential Diagnosis of Jaundice. Study of Two Hundred and Thirty-Five Cases of Nonhemolytic Jaundice Due to Carcinoma, Calculus in Common Bile Duct and Liver Degeneration, *Am J M Sc* **185** 358 (March) 1933.

38 Althausen, T. L., Gunther, L., Lagen, J. B., and Kerr, W. J. Modification of the Dextrose Tolerance Test as an Index of the Metabolic Activity of the Liver, *Arch Int Med* **46** 482 (Sept) 1930.

39 Migneco, G. Practical Value of New Test of Hepatic Function, *Policlinico (sez prat)* **40** 845 (May 29) 1933.

40 Ricketts, H. T. Function of Liver. Appraisal of Modified Dextrose Tolerance Test, *Arch Int Med* **52** 147 (July) 1933.

41 Rowe, A. W., Plummer, A. J., and McManus, M. A. The Metabolism of Levulose. I. Some Considerations on Provocative Levulosuria, *Am J M Sc* **186** 15 (July) 1933.

sized the variability of the tolerance even in normal persons, the difficulties in the use of changes in the amount of blood sugar to indicate divergences from the normal tolerance and the various physiologic factors, especially those of endocrine origin, which affect the use of tolerance to levulose as a test for hepatic disturbances

The levulose tolerance test, nevertheless, has its proponents, the most recent one is Kimball,<sup>42</sup> who reported on 430 patients. Three hundred and thirty of the patients had some degree of hepatic insufficiency, and 45 per cent of this group gave a positive reaction. Rao<sup>43</sup> likewise found that the levulose tolerance test gave positive results in a greater number of patients with disease of the liver than in those without evidence of hepatic disorder. Positive results were most frequent in cases in which there had been acute destruction of the hepatic parenchyma. In cases of cirrhosis, the results were more variable, presumably owing to the variable extent to which hepatic tissue had been regenerated. A negative reaction, therefore, does not exclude hepatic disease. Rao preferred levulose to galactose for the testing of hepatic function.

Galactose at the present time is the most popular sugar for use in the test for hepatic function. Zadek and his co-workers,<sup>44</sup> Banks, Sprague and Snell,<sup>45</sup> Tumen and Piersol,<sup>46</sup> Rosenberg,<sup>47</sup> Singer and Wechsler<sup>48</sup> and Schiff and Senior<sup>49</sup> reported on the study of this test in various types of hepatic disease with particular reference to the differential diagnosis of jaundice. All of these authors were agreed that a positive reaction, that is, a urinary excretion of more than 3 Gm., is indicative of diffuse parenchymal injury to the liver, but the results

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42 Kimball, S. The Levulose Tolerance Test. A Study of Its Value with Especial Reference to Mild and Chronic Disease of the Liver, *Guy's Hosp Rep* **82** 157 (April) 1932

43 Rao, M. V. R. Investigation into Clinical Values of Levulose and Galactose Tolerance Tests for Hepatic Function, *Indian J. M. Research* **21** 141 (July) 1933

44 Zadek, E., Tietze, A., and Gebert, K. Evaluation of Functional Tests of Liver at Bedside, *Klin. Wchnschr* **12** 60 (Jan. 14) 1933

45 Banks, B. M., Sprague, P. H., and Snell, A. M. Clinical Evaluation of the Galactose Tolerance Test, *J. A. M. A.* **100** 1987 (June 24) 1933

46 Tumen, H. J., and Piersol, G. M. Value of Alimentary Galactosuria in Diagnosis of Jaundice, *Ann. Int. Med.* **7** 311 (Sept.) 1933

47 Rosenberg, D. H. The Galactose and Urobilinogen Tests in the Differential Diagnosis of Obstructive and Intrahepatic Jaundice, *Ann. Int. Med.* **8** 60, 1934

48 Singer, K., and Wechsler, L. Clinical Significance and Pathogenic Mechanism of Agalactosuria, *Wien. klin. Wchnschr* **47** 77 (Jan. 19) 1934

49 Schiff, L., and Senior, F. A. A Study of One Hundred Cases of Jaundice with Particular Reference to Galactose Tolerance, *J. A. M. A.* **103** 1924 (Dec. 22) 1934



obtained in cases of the various types of disease were not uniform Schiff and Senior, for example, obtained positive reactions in over 93 per cent of the cases of acute toxic or infectious hepatitis, while negative results were uniformly the rule in cases of obstructive jaundice They, therefore, considered the test to be of great value in differentiating the two forms of jaundice Zadek, on the other hand, reported positive results in only 50 per cent of the cases studied Banks, Sprague and Snell obtained positive reactions in 83 per cent of their cases of acute hepatitis and in 38 per cent of those of obstructive jaundice They, therefore, insisted that while the test is of value it is not pathognomonic and that the results must be weighed against the other clinical findings in the individual case

Because of the possibility that variations in the rate of absorption of galactose from the intestine or in the excretion of galactose by the kidney will affect the results of the tolerance test as usually performed, Jankelson and Lerner<sup>50</sup> injected 25 Gm of sugar intravenously and then observed the changes in the galactose content of the blood Seven normal persons and 8 patients with hepatic disease were studied In the normal subjects the galactose disappeared from the blood stream within an hour Minimal degrees of hepatic damage were not shown, but in the presence of demonstrable damage the galactose was metabolized at a slower rate and retained in the blood Positive results were obtained in all the cases of jaundice, though the changes were most marked in those of hepatitis The series of cases reported, however, was too small to permit final conclusions regarding the diagnostic usefulness of this method of studying galactose tolerance

Pavel, Florian and Radvan<sup>51</sup> also studied the galactose test in a series of cases of jaundice They found that administration of insulin reduced the degree of galactosuria In addition, they studied the lipolytic activity of the pancreatic juice and the diastatic activity of the urine as guides to the secretion of the pancreas Changes which they interpreted as indicating pancreatic insufficiency were found in 15 of 17 cases of catarrhal jaundice Similar changes, though less frequent, were found in cases of hepatic cirrhosis Because the results of the galactose tolerance test paralleled the tests of pancreatic function, Pavel and his associates expressed the belief that the changes in galactose tolerance must be explained as due to pancreatic rather than to hepatic disturbances

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50 Jankelson, I R, and Lerner, H H Intravenous Galactose Liver Function Test Preliminary Report, *Am J Digest Dis & Nutrition* **1** 310 (July) 1934

51 Pavel, I, Florian, I, and Radvan, I Significance of Testing for Carbohydrates, Especially Galactose, in Functional Examination of Liver, *Ann de med* **35** 380 (May) 1934

The possibility of pancreatic involvement in association with hepatic disease was also emphasized by Michelazzi<sup>52</sup> who reported that the elevation of the blood sugar in a dextrose tolerance test is diminished if hydrochloric acid is given with the dextrose. He thought that the acid stimulates the production of pancreatic secretion and increases the production of both insulin and the external secretion of the pancreas. Foged<sup>53</sup> found a pathologic degree of diastasia in patients with biliary calculi or cholecystitis. This was ascribed to infection or irritation of the pancreas secondary to inflammatory changes in the biliary tract.

The measurement of pancreatic function is even more difficult than that of hepatic function. The evidence to date should not be accepted as entirely conclusive of these contentions, however, the possibility of pancreatic involvement is one which should ever be kept in mind in the study of patients with hepatic disease.

*Cholesterol and Cholesterol Esters of the Serum*—The value of the determination of cholesterol esters in the blood in cases of jaundice depends on the fact that, when taken in conjunction with the determination of the total cholesterol and bilirubin contents of the blood, it affords a method of distinguishing between jaundice due to biliary obstruction and that due to parenchymatous disease of the liver. Epstein<sup>54</sup> recently reported a comprehensive study of a large number of cases. In obstructive jaundice there is usually hypercholesteremia, which roughly parallels the degree of obstruction and bilirubinemia and returns to a normal level with the relief of the obstruction. The amount of cholesterol esters rises concomitantly with that of total cholesterol in about one-half the cases, in other cases (probably associated with greater damage to the liver) the value for cholesterol esters remains normal but lags relatively behind the increased content of free cholesterol. In cases of cholecystitis and cholelithiasis without obstruction, the blood cholesterol does not vary significantly.

In cases of degenerative diseases of the liver there is usually a marked divergence between the bilirubin and the cholesterol content of the blood. The more pronounced the damage to the liver, the greater the hypocholesteremia which accompanies the hyperbilirubinemia. In these cases the values of the cholesterol esters are even more depressed than that of the total cholesterol, and parallel the degree of hepatic

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52 Michelazzi, A. M. Action of Hydrochloric Acid on Glucemia of Hepatic Patients, *Polclimico (sez. med.)* **41** 78 (Feb) 1934.

53 Foged, J. Clinical Significance of Diastasia. III. Diastasia in Diseases of Biliary Tract, *Hospitaltid* **75** 1359 (Nov. 24) 1932.

54 Epstein, E. Z. Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, *Arch. Int. Med.* **50** 203 (Aug.) 1932.

damage even more accurately. A rise in the value of the cholesterol esters in such a case may be the first indication of an improved prognosis. Similar experiments have been reported by Mjassnikow<sup>55</sup>

*Changes in the Serum Proteins*—The problem of the disturbance in the coagulation of the blood and the tendency to hemorrhage in jaundice is an old one. Various theories have been proposed to explain the abnormal mechanism of coagulation in obstructive jaundice, and each in turn has been largely abandoned. The calcium theory has not proved tenable, repeated analyses having shown that the total and the "available" serum calcium of jaundiced subjects usually fall within normal limits. Likewise, normal values have been obtained for blood platelets, for plasma fibrinogen, for fibrin and even for the clotting time of the blood. The explanation in vogue at present is the presence in the blood stream of a substance or substances which interfere with the process of coagulation. In support of this view is the fact that in many jaundiced patients the blood clot, although forming with normal rapidity, is large, friable and nonretractile, as though syneresis of the fibrin had been inhibited. In contrast to the normal compact clot, a porous mesh of this kind may permit the seepage of cells and plasma from a damaged blood vessel, and this may lead to the slow, persistent exsanguination encountered in cases of obstructive jaundice. The interfering substances, according to Barlik,<sup>56</sup> may be in the nature of antithrombin or antiprothrombin. These terms are concerned with the mode of action of the interfering material, but they tell nothing regarding its origin or chemical nature. Information bearing on this point is supplied by the recent investigation of Carr and Foote.<sup>57</sup> Bile is an excretory medium for a variety of substances which, as a result of biliary obstruction, may accumulate in the blood stream. Disturbances in the metabolic activity of the liver from the same cause also may lead to the accumulation in the blood stream of abnormal products of metabolism or to failure of the processes of removal or detoxification of toxic byproducts of the normal processes of metabolism.

An observation of Mueller and Sturgis<sup>58</sup> that cysteine inhibits coagulation of the blood induced Carr and Foote to study the possible

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55 Mjassnikow, A. L. Role of Liver in Cholesterol Metabolism. *Klin Wchnschr* **11** 1910 (Nov 12) 1932.

56 Barlik, A. Delayed Blood Coagulability in Obstructive Jaundice. *Arch f klin Chir* **176** 252 (Sept 20) 1933.

57 Carr, J. L., and Foote, F. S. Progressive Obstructive Jaundice. Changes in Certain Elements of the Blood and Their Relation to Coagulation, *Arch Surg* **29** 277 (Aug) 1934.

58 Mueller, I. H., and Sturgis, S. Prevention of Blood Coagulation by Cysteine, *Science* **75** 140 (Jan 29) 1932.

relation of this amino-acid to the impaired clotting reaction in obstructive jaundice. Preliminary studies demonstrated that the addition of minute amounts of cysteine to normal blood shortened the coagulation time but changed the clot to a large, friable, nonretractile one, closely resembling that formed in the blood of jaundiced human subjects. The injection of large doses of cysteine into normal animals produced a similar effect. Color tests for cysteine demonstrated that none was present in normal plasma, whereas definite reactions were obtained on the plasma from jaundiced animals. Furthermore, the intensity of the test increased progressively with the tendency to hemorrhage.

The foregoing indications that cysteine, or perhaps a related mercaptan, is intimately related to the abnormal clotting reaction in jaundiced subjects prompted an investigation of the therapeutic action of brombenzene, a substance that combines with cysteine to form bromphenylmercapturic acid, which is excreted in the urine. The tendency toward bleeding was definitely reduced in the treated animals, and they did not die of hemorrhage. Crystals of bromphenylmercapturic acid were isolated from the urine.

This investigation, if confirmed, undoubtedly will constitute a valuable contribution to the current knowledge of the etiology of the hemorrhagic tendency in obstructive jaundice, but much more experimental work on the subject is needed before conclusions can be drawn. Likewise, although the beneficial action of brombenzene therapy is at least suggestive, it should be recalled that this substance is definitely toxic and should be used with the greatest caution. Perhaps of most immediate clinical import is the suggestion that an excess of protein, the metabolic precursor of cysteine and related mercaptans, should be avoided in the diet of patients with obstructive jaundice.

Whipple and his associates<sup>59</sup> showed that the liver is concerned with the formation of the various blood proteins. This is true not only of fibrinogen but perhaps of serum albumin and serum globulin as well. There is an increasing literature dealing with changes in the serum globulin. Most of this evidence, however, is indirect and was obtained by means of the sedimentation rate or by flocculation reactions.

No attempt will be made to review the sedimentation rate in relation to disease in general or the various factors which affect this test. Linton<sup>60</sup> considered an increase in the sedimentation rate the best index to the danger of postoperative hemorrhage in jaundiced patients. Clute

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59 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Regeneration Controlled by Diet. I. Liver and Casein as Potent Diet Factors, *J. Exper. Med.* **59** 251 (March) 1934.

60 Linton, R. R. The Sedimentation Rate of Blood as an Index of the Haemorrhagic Tendency in Obstructive Jaundice, *Ann. Surg.* **91** 694 (May) 1930.

and Veal,<sup>61</sup> Burke and Weir<sup>62</sup> and Picardi,<sup>63</sup> on the other hand, expressed the belief that the results were too variable to make the test of prognostic value

Disturbances in the quality of the serum proteins can also be shown by various precipitation tests. One of these, the Takata-Ara test, is made with a dilute solution of colloidal mercuric chloride. A positive result presumably indicates an increase in the globulin, particularly in the euglobulin fraction, of the serum, with a shift or an inversion of the albumin-globulin ratio, though Schindel<sup>64</sup> thought that the appearance of the lower forms of fatty acids in the serum may play a rôle in the production of a positive reaction. It is generally agreed<sup>65</sup> that while a negative reaction does not rule out hepatic disease, nevertheless a positive result is strongly indicative of the condition. The test is of particular value in cases of advanced parenchymatous damage, such as cirrhosis, in which the percentage of positive reactions varies from 68 (Rohrer<sup>65a</sup>) to 84 per cent (Schindel and Barth<sup>65b</sup>). In cases of other conditions such as fatty degeneration, syphilis, acute hepatitis or chronic passive congestion, a positive reaction may be given, though much less frequently. A negative reaction is the rule in uncomplicated cases of

61 Clute, H. M., and Veal, J. R. The Prediction of Haemorrhage in Obstructive Jaundice by the Sedimentation Rate, *Ann Surg* **96** 385, 1932

62 Burke, C. F., and Weir, J. F. The Hemorrhagic Tendency in Jaundice. A Study of the Blood Fibrin, Sedimentation Rate, Coagulation Time, and Other Blood Factors, *J Lab & Clin Med* **18** 657 (April) 1933

63 Picardi, G. Erythrocyte Sedimentation Speed in Surgical Diseases of Biliary Tract, *Polichinico (sez prat)* **40** 1369 (Aug 28) 1933

64 Schindel, L. Mechanism of Takata-Ara Test, *Klin Wchnschr* **13** 221 (Feb 10) 1934

65 (a) Rohrer, C. Takata-Ara Reaction (Jezler Modification) in Diseases of Liver, *Ztschr f klin Med* **123** 637 (March 10) 1933. (b) Skouge, E. Clinical Contribution to Latent Liver Diseases, Especially Latent Cirrhosis of Liver, *Norsk mag f lægevidensk* **94** 393 (April) 1933. (c) Tannenholz, H. Takata Serum Reaction as Diagnostic and Prognostic Aid in Syphilology and Dermatology, *Am J Syph* **17** 352 (July) 1933. (d) Hugonot, G., and Sohler, R. Takata-Ara Reaction. Test of Hepatic Insufficiency, *Rev med-chir d mal du foie* **9** 5 (Jan-Feb) 1934. (e) Lazzaro, G. Reaction of Takata-Ara in Serum and Ascitic Fluid of Diseases of Liver, *Polichinico (sez med)* **41** 144 (March) 1934. (f) Crane, M. P. A Modified Mercuric Chloride Reaction (Takata-Ara) in Cirrhosis and in Neoplasm of the Liver, *Am J M Sc* **187** 705 (May) 1934. (g) Jezler, A. Clinical Experiences with Modified Takata Reaction, *Klin Wchnschr* **13** 1276 (Sept 8) 1934. (h) Schindel, L., and Barth, E. Significance of Takata Reaction for Diagnosis of Liver Diseases in Its Relation to Galactose and Bilirubin Tolerance Test, *Klin Wchnschr* **13** 1355 (Sept 22) 1934. (i) Heath, C. W., and King, E. F. The Takata-Ara Test in the Diagnosis of Liver Disease, *New England J Med* **211** 1077, 1934

obstructive jaundice, carcinoma or, according to Neuweiler,<sup>66</sup> the toxicoes of pregnancy

Seroreactions similar in character to the Takata-Ara reaction are those of Weltmann and Sieder<sup>67</sup> and the magnesium chloride test of Bauer<sup>68</sup>. In the former test 0.1 cc of serum is added to each of a series of tubes containing 4 cc each of solutions of various concentrations (from 0.1 to 0.01 per cent) of calcium chloride in distilled water. The serum is then coagulated by heating in a boiling water bath for fifteen minutes. Weltmann and Sieder<sup>67</sup> reported that the test is of value in the recognition of parenchymal injury to the liver, and this was confirmed by Massobrio and de Michelis<sup>69</sup> and by Pellegrini and Barsini<sup>70</sup>. The latter authors obtained positive reactions in cases of pernicious anemia, diabetes mellitus and chronic alcoholism, in which they thought that changes in hepatic function may occur.

The magnesium chloride test of Bauer is based on the addition of a 15.68 per cent solution of magnesium chloride to an equal volume of diluted serum. The solution is then heated on the water bath. Here, too, flocculation depends on an increase in the proportion of globulin in the serum. The majority of positive reactions were obtained in cases of hepatic cirrhosis or acute hepatic injury. Positive results were also the rule in cases of pernicious anemia. On the other hand, in cases of carcinoma, tuberculosis, syphilis and the like, negative reactions were the rule. Bauer considered this test of similar import to the Takata-Ara reaction but preferable because it is more sensitive and specific.

*Phosphatase Content of the Blood Serum*—Enzymes which hydrolyze esters of phosphoric acid or phosphatases are observed in many mammalian tissues, including the liver. They are also present in the bile. Roberts<sup>71</sup> found the phosphatase content of the serum increased in a

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66 Neuweiler, W. Takata Reaction and Pregnancy Toxiosis, *Klin Wchnschr* **13** 1428 (Oct 6) 1934

67 Weltmann, O., and Sieder, B. Significance of Weltmann's Coagulation Band for Diagnosis of Hepatic Disease, *Wien Arch f inn Med* **24** 321 (Feb 10) 1934

68 Bauer, R. Magnesium Chloride Test. New Reaction for Serum Proteins, *Med Klin* **30** 230 (Feb 16) 1934

69 Massobrio, E., and de Michelis, U. Serum Coagulation of Weltmann in Hepatopathy in Relation to Protein Picture of Serum, *Minerva med* **1** 147 (Feb 3) 1934

70 Pellegrini, M., and Barsini, G. Behavior and Significance of Weltmann's Serum Reaction in Some Diseases. Research on Behavior of Electrolytic Threshold of Coaguloflocculation to Heat of Exudates, Transudates and of Normal and Pathologic Cerebrospinal Fluid, *Minerva med* **1** 154 (Feb 3) 1934

71 Roberts, W. M. Variations in the Phosphatase Activity of the Blood in Disease, *Brit J Exper Path* **11** 90, 1930, Blood Phosphatase and the van den Bergh Reaction in the Differentiation of the Several Types of Jaundice, *Brit M J* **1** 734, 1933

series of cases of obstructive jaundice, whereas in cases of toxic, infectious or catarrhal jaundice the values were only slightly increased over the normal content. He therefore considered the test of value in differential diagnosis. Bodansky and Jaffe<sup>72</sup> and Armstrong, King and Harris<sup>73</sup> found that the serum phosphatase was markedly increased in experimental obstructive jaundice. However, Bodansky and Jaffe<sup>74</sup> also obtained high values in cases of hepatitis. Greene, Shattuck and Kaplowitz<sup>75</sup> reinvestigated the problem and found that phosphatase was present in samples of bile obtained from the gallbladder at operation or by duodenal intubation.

The phosphatase content of the serum was increased in cases of jaundice due to hepatitis or to obstruction of the biliary passages. This test was of no value in the differential diagnosis of the two conditions. The phosphatase content of the serum was not increased in cases of hemolytic jaundice but was increased in cases of portal cirrhosis.

*Miscellaneous Tests of Hepatic Function*—A multitude of tests designed to show changes in hepatic function have been described, and the number increases almost daily. De Flora<sup>76</sup> found that the ketone bodies in the blood of normal persons were increased for a period of from one to two hours after the ingestion of sugar. The level of the ketone bodies in the blood during fasting in patients with hepatic disease was higher than in normal persons, but it did not increase after the ingestion of sugar. Quick<sup>77</sup> reported that the synthesis of hippuric acid was diminished in patients with hepatic damage. It is also reduced in cases of nephritis, but Quick considered the test a valuable aid in the diagnosis of hepatic disease. Caccuri and Chiariello<sup>78</sup> injected amino-acetic acid intravenously and studied the changes in the amino-acid in

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72 Bodansky, A., and Jaffe, H. L. Increase of Serum Phosphatase After Bile Duct Ligation in Dog, *Proc Soc Exper Biol & Med* **31** 1179 (June) 1934.

73 Armstrong, A. R., King, E. J. and Harris, R. I. Serum Phosphatase in Obstructive Jaundice, *Canad M A J* **31** 14 (July) 1934.

74 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. IV. Serum Phosphatase of Non-Osseous Origin. Significance of the Variations of Serum Phosphatase in Jaundice, *Proc Soc Exper Biol & Med* **31** 107, 1933, Significance of Clinical and Experimental Serum Phosphatase Variations, Their Osseous and Non-Osseous Origins, *J Biol Chem* **105** 21, 1934.

75 Greene, C. H., Shattuck, H. F., and Kaplowitz, L. The Phosphatase Content of the Blood Serum in Jaundice, *J Clin Investigation* **13** 1079 (Nov) 1934.

76 de Flora, G. Ketonemic Curve After Ingestion of Sugar as Test of Hepatic Function, *Riforma med* **12** 804 (May 24) 1934.

77 Quick, A. J. Synthesis of Hippuric Acid. New Test of Liver Function, *Am J M Sc* **185** 630 (May) 1933.

78 Caccuri, S., and Chiariello, A. New Procedure of Functional Examination of Liver. Deaminizing Power of Liver After Glyocoll Injection, *Arch d mal de l'app digestif* **24** 840 (Oct) 1934.

the blood. A pathologic curve for the amino-acetic acid content of the blood and a delay in the removal from the blood stream of the injected amino-acid were reported in a series of patients with hepatic disease. Similar changes were observed in rabbits after the experimental administration of various hepatic poisons.

Monguió and Krause<sup>79</sup> found that the ammonia in the blood was increased in dogs with various types of hepatic injury. They considered that this was evidence of disturbance in the ureagenic function of the liver and that it furnished experimental evidence in support of the clinical use of high carbohydrate diets in diseases of the liver.

Nakagawa, Imuro and Suzuki<sup>80</sup> injected 1.5 cc. of a 20 per cent solution of bile acid intravenously. Specimens of urine were then collected every thirty minutes for a two hour period. The reaction was considered positive if the urine showed a white turbidity following the addition of acetic acid, a positive Hay reaction and an increased content of urobilin or urobilinogen over that of the control. They believed that this is a sensitive test and that it shows functional impairment of slight degree. At the same time, it is of correspondingly less value for the differentiation of various types of hepatic lesions.

It has long been accepted that the clinical picture in the various types of jaundice is not always distinct. The same confusion is true of the pathologic changes, for many cases of chronic cholecystitis show accompanying hepatitis of varying degrees of severity. Infection may be absent in cases of biliary obstruction due to carcinoma of the head of the pancreas, but the resultant hydrohepatosis is responsible for parenchymal atrophy or the development of obstructive cirrhosis. The varieties of hepatogenous jaundice have been mentioned. When the different factors are taken into consideration it becomes obvious that the grouping of cases of jaundice into hepatic and obstructive types, as is done in clinical practice, is essentially arbitrary. It appears to us<sup>81</sup> that continuance of the search for functional tests which will distinguish specifically between the two groups of cases is not likely to be successful. The value of the present tests is not determined by the percentage of occurrence of positive results in cases of the hepatic and obstructive types of jaundice. Functional tests rather should be used in an attempt to determine the extent to which the various elements already referred to enter into the clinical picture.

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79 Monguió, J., and Krause, F. Significance of Ammonia Content of Blood for Estimation of Liver Function, *Klin Wchnschr* **13** 1142 (Aug 11) 1934.

80 Nakagawa, S., Imuro, S., and Suzuki, S. Bile Acid Tolerance Test for Determination of Hepatic Function, *Klin Wchnschr* **13** 1392 (Sept 29) 1934.

81 Greene, C. H., and Shattuck, H. F. The Clinical Use of Tests of Hepatic Function, *Am J Digest Dis & Nutrition* **1** 505 (Sept) 1934.



## FUNCTIONAL DISTURBANCES IN EXOPHTHALMIC GOITER AND PREGNANCY

Disturbances in hepatic function have been reported in a variety of diseases. The cause of the jaundice occasionally seen in patients with hyperthyroidism has been a subject of controversy. Schneider and Widmann,<sup>82</sup> Weller<sup>83</sup> and Beaver and Pemberton<sup>84</sup> have reported the occurrence of hepatic damage with degenerative changes, necrosis, subacute atrophy or moderate degrees of cirrhosis in patients with hyperthyroidism or exophthalmic goiter. Lichtman<sup>85</sup> also demonstrated that the oxidation of cinchophen is disturbed in such cases. He considered this test indicative of functional impairment, perhaps secondary to the depletion of glycogen in the cells of the liver.

The pathogenesis of eclampsia is by no means clear, but because pathologic changes are frequently noted in the liver there has been a great deal of interest in the results of functional tests during normal pregnancies and in patients with eclampsia. Hofbauer<sup>86</sup> and Soffer<sup>87</sup> found that the elimination of injected bilirubin was normal during the first half of the pregnancy but that there was a definite retention during the second half. Germer<sup>88</sup> studied the quinine-resistant lipase in the serum as an index of hepatic function. Positive reactions were the rule after the sixth or seventh month with a return toward normal levels just before delivery. The urobilinogen in the urine showed comparable changes. Huwer,<sup>89</sup> on the other hand, did not consider urobilinuria sufficiently marked to indicate impairment of the liver. Cantarow, Stuckert and Gartman<sup>90</sup> found normal values for the serum bilirubin. Retention of bromsulphalein was present in some but not

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82 Schneider, E, and Widmann, E. Clinical and Experimental Studies of Goiter Problem and of Exophthalmic Goiter, *Deutsche Ztschr f Chir* **241** 15 (July 22) 1933

83 Weller, C V. Hepatic Pathology in Exophthalmic Goiter, *Ann Int Med* **7** 543 (Nov) 1933

84 Beaver, D C, and Pemberton, J deJ. Pathologic Anatomy of Liver in Exophthalmic Goiter, *Ann Int Med* **7** 687 (Dec) 1933

85 Lichtman, S S. Liver Function in Hyperthyroidism, *Arch Int Med* **50** 721 (Nov) 1932

86 Hofbauer, J. Hepatopathy of Pregnancy and Pathogenesis of Eclampsia, *Zentralbl f Gynak* **57** 35 (Jan 7) 1933

87 Soffer, L J. Bilirubin Excretion as Test for Liver Function During Normal Pregnancy, *Bull Johns Hopkins Hosp* **52** 365 (May) 1933

88 Germer, K. Comparative Investigations on Liver Function in Normal Pregnant Women, *Ugesk f læger* **95** 495 (April 27) 1933

89 Huwer, G. Blood Pigment Metabolism in Gestation. Function of Liver During Pregnancy, *Ztschr f Geburtsh u Gynak* **106** 324 (Oct 13) 1933

90 Cantarow, A, Stuckert, H, and Gartman, E. Studies of Hepatic Function. IV Hepatic Function During Pregnancy, *Am J Obst & Gynec* **29** 36 (Jan) 1935

in all of the cases of eclampsia. They agreed with Dietel and Polak<sup>91</sup> that hepatic damage in eclampsia is more frequent than is indicated by the tests of hepatic function. Stander and Cadden<sup>92</sup> considered a rise in the uric acid content of the blood the best diagnostic criterion in pre-eclamptic states. They thought it evidence of hepatic disturbance, but the exact mechanism was not understood.

#### HEPATIC CIRRHOSIS

The present tendency is to divide cirrhotic processes in the liver into portal cirrhosis and obstructive biliary cirrhosis. In the past there have been many classifications of cases of portal cirrhosis into subgroups on an etiologic or a morphologic basis or on the basis of presumed differences in the clinical picture. The majority of such classifications have not been satisfactory, and the present tendency, as pointed out by Moon,<sup>93</sup> is to use the term "cirrhosis" as synonymous with "chronic diffuse hepatitis." Any agent or combination of agents which produces chronic diffuse hepatic inflammation results in some degree of cirrhosis. The degree and character of the cirrhosis may vary, but the essential features of the cirrhotic process are (1) degeneration and destruction of liver cells, (2) regeneration of hepatic cells from those which escaped destruction and (3) proliferation of connective tissue.

Moon, who reviewed the literature on experimental cirrhosis in an attempt to evaluate the bearing of these experiments on cirrhosis in man, pointed out that numerous agents, diverse in character, are capable of causing degeneration and necrosis of hepatic cells. These agents include various chemicals, both organic and inorganic, certain drugs and tarlike substances, foreign proteins and products of protein decomposition, bacterial products, immune serums and infections. The continued or repeated action of these agents has resulted in the production of chronic diffuse hepatitis, as indicated by degeneration and necrosis, regeneration of parenchyma and proliferation of fibrous tissue.

Probably the majority of these agents have no etiologic significance in the development of cirrhosis in man. Yet the results of the investigation of their action have contributed greatly to an understanding of the mechanism by which cirrhosis develops. In every instance in which the prolonged action of an agent has resulted in a degree of cirrhosis,

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91 Dietel, F. G., and Polak, A. Late Disturbances of Functions of Liver and Reticulo-Endothelial System After Eclampsia, *Arch f Gynak* **152** 469 (Feb. 22) 1933.

92 Stander, H. J., and Cadden, J. F. Acute Yellow Atrophy of the Liver in Pregnancy, *Am J Obst & Gynec* **28** 61 (July) 1934, Blood Chemistry in Pre-Eclampsia and Eclampsia, *ibid* **28** 856 (Dec.) 1934.

93 Moon, V. H. Experimental Cirrhosis in Relation to Human Cirrhosis, *Arch Path* **18** 380 (Sept.) 1934.

the acute effects have been degeneration and necrosis of hepatic cells. Cirrhosis, like other chronic inflammations, results from parenchymatous injury followed by repair. If such injury is severe, continued or repeated, repair will be accompanied by fibrosis. This evidence should tend to allay a controversy of long duration between certain groups of European pathologists.

A few agents which have met satisfactorily the rigid criteria for the production of Laennec's cirrhosis are phosphorus and alcohol, manganese chloride with phenylhydrazine, carbon tetrachloride, tars, bacterial infections and combinations of infection and other agents. Each of these agents has produced distortion of the architecture of the organ, in which marked alteration of the lobular pattern was evident. The islands of regenerated hepatic cells occurred as nodules rather than as lobules and indicated the type of circulatory disarrangement which is characteristic of Laennec's cirrhosis. In experiments with carbon tetrachloride, the circulatory disturbances resulted in portal circulatory obstruction, as indicated by ascites and by the development of collateral venous channels.

The belief that cirrhosis is caused by alcohol has not received experimental support. Without exception, the agents which have produced cirrhosis experimentally have caused hepatic necrosis. Alcohol, even in large amounts and with long-continued use, has caused only parenchymatous degeneration and fatty changes. These changes have resulted neither in necrosis nor in permanent hepatic changes. However, the probability that alcohol acts as a contributing or predisposing factor has received experimental support. Alcohol has been found to accentuate the injurious effects of bacteria, phosphorus, chloroform and carbon tetrachloride on the liver of animals. It is probable that alcohol may similarly accentuate the effects of injurious agents on the human liver. By virtue of this property, alcohol may be an important contributory factor in the development of human cirrhosis.

Cirrhosis resulting from treatment with tar has duplicated Laennec's cirrhosis with remarkable accuracy. The gross and microscopic characteristics have fulfilled the rigid requirements. The splenic changes have resembled those accompanying Laennec's cirrhosis, and ascites has been an almost constant associated feature. The fact that the experiments were made on rabbits makes a high degree of conservatism necessary in their interpretation. However, the high percentage of positive results makes it probable that coccidiosis was not concerned. In some experiments, erroneous conclusions were partially obviated by examinations of the liver prior to experimentation.

The injurious effects of hydrazine and similar organic chemicals and the production of cirrhosis by means of tars have perhaps a deeper sig-

nificance than is apparent. Many investigators have expressed the belief that various substances present incidentally in alcoholic liquors may be responsible for the cirrhosis occurring among drinkers of these beverages. Many such contaminants have been investigated without significant results. The tarlike products or substances of the benzene series formed by the charring of casks used for the aging of liquor have not been investigated. Liquors aged in charred casks contain visible quantities of a brownish substance dissolved from the semichaired wood. Such substances might produce effects similar to those of tars. Is it possible that such substances may be responsible for the development of cirrhosis in habitual drinkers of alcoholic liquors?

There is evidence that metabolic disturbances may be important contributing factors. Medical literature contains records of many observations on the simultaneous occurrence of exophthalmic goiter and cirrhosis. A survey of the occurrence of cirrhosis in different sections of the United States showed a suggestive relationship between cirrhosis and disease of the thyroid gland. The states having the highest death rate from disease of the thyroid had also the highest death rate from cirrhosis. A similar relationship is exemplified in European countries. The highest incidence of cirrhosis on record is in Switzerland, where goiter also is most prevalent. Livers with low glycogen content have an increased susceptibility to injury. Hyperthyroidism may contribute to the development of cirrhosis by producing hepatic glycopenia. Marked thyrotoxicosis produces extensive hepatic necrosis. Hence thyrotoxicosis may be a direct cause of cirrhosis.

Infections in animals are known to cause hepatitis which closely resembles Laennec's cirrhosis. The high incidence of cirrhosis in tropical countries, associated with infectious diseases peculiar to those regions, is significant. It is admitted that congenital syphilis may result in a form of cirrhosis resembling that bearing the name of Laennec. Many observers have demonstrated a relationship between streptococcal infection and cirrhosis. It is probable that chronic diffuse infections of the liver are important factors in the etiology of cirrhosis.

It is significant that combinations of agents have been found more effective in the production of cirrhosis than any of the agents alone. The combination of alcohol with phosphorus, of manganese chloride with colon bacilli or with hydrazine, of chloroform with alcohol, cholesterol, streptococci or colon bacilli, and of alcohol with bacteria or with carbon tetrachloride and the effect of diet in experiments with phosphorus, chloroform and carbon tetrachloride are important examples. The results in such instances suggest the importance of combinations of agents in the etiology of cirrhosis in man.

A survey of experimental and clinical studies on cirrhosis convinces one that no single causative factor is responsible. Cirrhosis is synon-

ymous with chronic progressive hepatitis. Its etiology will be found to be as variable as are the agents which, singly or in combination, may cause chronic diffuse progressive inflammation of the liver.

While Moon was concerned primarily with the study of experimental forms of cirrhosis, the view is in accord with those of Althausen<sup>94</sup> and of Menne and Johnston,<sup>95</sup> who were interested in the clinical features of the condition.

Various clinical reports have presented cases which further stress the similarity between the clinical and experimental forms of cirrhosis. The report of Yenikomshian<sup>96</sup> is of interest in emphasizing the frequency of cirrhosis in a population in which the use of alcohol is taboo. He expressed the belief that chronic infection, produced by chronic malaria or amebic dysentery or by a combination of the two, is primarily responsible for the frequency of cirrhosis in Syria and Lebanon. Poindexter and Greene<sup>97</sup> reported a case of portal cirrhosis which was due to long continued exposure to the fumes of carbon tetrachloride and could be considered the clinical counterpart of the cirrhosis experimentally produced in animals by the action of this substance. The rôle of cinchophen and of cinchophen derivatives in producing toxic hepatitis or subsequently hepatic cirrhosis has been brought to the attention of clinicians during the past few years. The literature on this subject has been reviewed by Weir and Comfort<sup>98</sup> and by Bloch and Rosenberg<sup>99</sup>.

McCartney<sup>100</sup> reviewed the observations in a series of 245 cases of portal cirrhosis detected in routine postmortem examinations. There was an incidence of 2.05 per cent, which agreed well with that of 1.36 per cent reported by Menne and Johnson. The weight of the liver was much more variable than in normal persons, though there was a disproportionately large number of hypertrophic livers occurring in the earlier decades of adult life and of atrophic livers in persons in the later

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94 Althausen, T. L. Etiology and Pathogenesis of Hepatic Cirrhosis, *Ann Int Med* **6** 1080 (Feb.) 1933.

95 Menne, F. R., and Johnston, T. W. Cirrhosis of Liver. Its Character and Incidence in Six Thousand Five Hundred Autopsies, *Northwest Med* **32** 129 (April) 1933.

96 Yenikomshian, H. A. Nonalcoholic Cirrhosis of the Liver in Lebanon and Syria, *J. A. M. A.* **103** 660 (Sept. 1) 1934.

97 Poindexter, C. A., and Greene, C. H. Toxic Cirrhosis of the Liver. Report of a Case Due to Long Continued Exposure to Carbon Tetrachloride, *J. A. M. A.* **102** 2015 (June 16) 1934.

98 Weir, J. F., and Comfort, M. W. Toxic Cirrhosis Caused by Cinchophen, *Arch Int Med* **52** 685 (Nov.) 1933.

99 Bloch, L., and Rosenberg, D. H. Cinchophen Poisoning. A Report of Seven Cases with Special Reference to a Rare Instance Complicated by Multiple Gastric Ulcers, *Am J Digest Dis & Nutrition* **1** 433 (Sept.) 1934.

100 McCartney, J. S. Latent Portal Cirrhosis of the Liver, *Arch Path* **16** 817 (Dec.) 1933.

decades. Livers which showed the more advanced degrees of cirrhosis tended to be smaller than those in which the process was less advanced.

Hijmans, van den Bergh and Kamerling<sup>101</sup> and Fellingner and Klima,<sup>102</sup> among others, emphasized the tendency to anemia in portal cirrhosis. This anemia, which is typical of the advanced cases of cirrhosis, is macrocytic in type with an increased color index and morphologic changes in the blood cells resembling those seen in pernicious anemia. The authors therefore expressed the belief that a hepatic element may be present in pernicious anemia, and they discussed at length the possible interrelationship of cirrhosis and anemia.

The treatment of cirrhosis has undergone little change during the period under consideration. The elimination of the causative agent when it can be identified, diets high in carbohydrate and low in salt or with an acid ash and the use of ammonium or potassium salts frequently in combination with mercurial diuretics, such as salyrgan, are the measures most in favor. McCabe and Hart,<sup>103</sup> among others, advocated the use of large doses of insulin in addition, but the good results which they reported could be ascribed equally to the use of a carbohydrate diet. Certainly the majority of patients with hepatic cirrhosis, with the exception of those with hemochromatosis, show no clinical signs suggesting the presence of diabetes or a failure in the supply of insulin. McCartney reported that in 35 per cent of the cases which he studied the cirrhosis was latent and had not been recognized chemically. Perhaps the most important factor in the management of cirrhosis, as stressed by Althausen and by Chapman, Snell and Rowntree,<sup>104</sup> is its early recognition and treatment before the development of ascites or the production of irreparable hepatic damage.

#### HEPATOSPLENOGRAPHY

When a colloidal solution of thorium dioxide is injected intravenously, the particles of thorium dioxide which are opaque to the roentgen rays are phagocytosed by the histiocytic cells of the reticulo-endothelial system. The roentgenographic demonstration of structural changes in

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101 van den Bergh, A. A., Hijmans and Kamerling, A. W. C. G. Cirrhosis of Liver with Hemolytic Anemia and Severe Hematinemia, *Nederl tijdschr v geneesk* **78** 4432 (Sept. 29) 1934.

102 Fellingner, K., and Klima, R. Studies on Anemias in Cirrhosis of Liver, *Wien klin Wchnschr* **46** 1191 (Oct. 6) 1933.

103 McCabe, J., and Hart, J. F. Treatment of Hepatic Cirrhosis with Insulin. Preliminary Report with Case Histories, *New York State J. Med* **33** 1924 (Aug. 1) 1933.

104 Chapman, C. B., Snell, A. M., and Rowntree, N. Compensated Cirrhosis of the Liver. A Plea for More Intensive Consideration of the Earlier Stages of Disease of the Hepatic Parenchyma, *J. A. M. A.* **100** 1735 (June 3) 1933.

the liver and spleen is thereby made possible. The extensive literature on this technic has been extended during the past two years by the reports of Reeves and Apple,<sup>105</sup> Ericksen and Rigler<sup>106</sup> and Yater and Otell.<sup>107</sup> The last two reports of Yater and Otell<sup>107b</sup> dealt with series of 82 and 100 cases, respectively. All these authors were in agreement that the method is of value in detecting the nature of a mass in the upper part of the abdomen, in the preoperative recognition of hepatic metastases in cases in which an operation for cancer, particularly of the gastro-intestinal tract, is contemplated, in the diagnosis of hepatic disease and in the recognition of such conditions as cirrhosis, gumma, abscess, cyst or primary tumor of the liver.

Ericksen and Rigler and Yater and Otell called attention to the report of the Council on Pharmacy and Chemistry of the American Medical Association<sup>108</sup> and urged caution in the intravenous use of thorium dioxide because it is a heavy metal and insoluble after being phagocytosed by the reticulo-endothelial cells and because its excretion is slow and probably requires years to be completed, if it ever is. Thorium is radioactive, and while the total dose of alpha rays is slight (equivalent to from 1.5 to 3 micrograms of radium) and no immediate harmful effects, either local or general, have been observed, the possibility of remote effects cannot be excluded. Shute and Davis,<sup>109</sup> in addition, reported that in rabbits and dogs large doses of thorium dioxide produced temporary degenerative changes in both the liver and the spleen. While the doses of thorium dioxide used in clinical practice are well within the apparent limit of safety of this procedure, it is probably wisest for the present to follow the suggestion of Yater and Otell and employ hepatosplenography only on the patients who are subjects of a rapidly fatal disease.

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105 Reeves, R. J., and Apple, E. D. The Use of Thorium Dioxide in the Diagnosis of Liver Abscess, *J. A. M. A.* **100** 1682 (May 27) 1933.

106 Ericksen, L. G., and Rigler, L. G. Roentgen Visualization of Liver and Spleen with Thorium Dioxide Sol, with Particular Reference to the Preoperative Diagnosis of Carcinomatous Metastases to the Liver, *J. A. M. A.* **100** 1758 (June 3) 1933.

107 (a) Yater, W. M. Diagnosis of Diseases of Liver, with Especial Reference to Thorotrast Hepatosplenography, *M. Ann. District of Columbia* **2** 156 (July) 1933. (b) Yater, W. M., and Otell, L. S. Differential Diagnosis of Diseases of Liver and Spleen with Aid of Roentgenography After Intravenous Injection of Thorium Dioxide Sol (Thorotrast). Experience with Eighty Patients, *Ann. Int. Med.* **7** 381, 1933. Hepatosplenography with Thorium Dioxide Sol. Clinical Experience with One Hundred Patients, *J. A. M. A.* **101** 507 (Aug. 12) 1933.

108 Thorotrast, Report of Council on Pharmacy and Chemistry, *J. A. M. A.* **99** 2183 (Dec. 24) 1932.

109 Shute, E., and Davis, M. E. Histologic Changes in Rabbits and Dogs Following Intravenous Injection of Thorium Preparations, *Arch. Path.* **15** 27 (Jan.) 1933.

## News and Comment

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### AMERICAN HEART ASSOCIATION, INC

The Eleventh Scientific Session of the American Heart Association will be held on Tuesday, June 11, 1935, at the Hotel Claridge, Atlantic City, N J. The program will be devoted to various phases of cardiovascular disease.

### COMING MEETINGS

The American Society for Clinical Investigation will meet on May 6 at the Hotel Chalfonte-Haddon Hall, Atlantic City.

The Association of American Physicians will meet at the Hotel Chalfonte-Haddon Hall, Atlantic City, on May 7 and 8.

### METHODIC CAMPAIGN AGAINST RHEUMATISM

The Ligue Internationale contre le Rhumatisme will hold its fifth congress at Lund, Sweden, in September 1936.

Dr S Ingvar, professor of internal medicine at Lund, is chairman, and Prof Dr G Kahlmeter of Stockholm is secretary.



## Book Reviews

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**A Manual of the Practice of Medicine** By A. A. Stevens, M.D. Thirteenth edition Price, \$3.50 Pp 685 Philadelphia W. B. Saunders Company, 1934

In 1892, Dr. Stevens, then an instructor in physical diagnosis in the University of Pennsylvania, published the first edition of this manual. It was written at the request of many students, with the hope that it would serve as an outline of the practice of medicine "which shall be enlarged upon by diligent attention upon lectures and critical observations at the bedside." It proved a successful venture, for the fourth edition appeared in 1896. This edition was reviewed in *The Journal of the American Medical Association* (28:664 [April 3] 1897). The reviewer commented: "This little manual has reached its fourth edition—evidence of merit. Its author understands the art of constructing a clear and fairly comprehensive abstract of the contents of the larger works of medicine, to which due reference is made in the preface. The result is a convenient pocket companion that will be found useful by the student who is preparing a cram for examination, or even by the newly fledged professor who is about to step forth into the arena. But for students who are engaged in class-work such hand-books are too sketchy, and, consequently, dry and uninteresting—mere skeletons, devoid of attraction."

The life history of the book is of some interest. During its first ten years of existence six editions were necessary, during its second ten years four editions and during its third ten years three editions. These figures suggest, perhaps, that with the passage of time and the changing trends in medical education students no longer cram for examinations as they did, newly fledged professors are less diffident about stepping forth into the arena than they were, and there is less demand for this kind of a compendium.

However, this thirteenth edition, like its predecessors, appears as a well articulated volume. It is deliberately sketchy but very much up to date, containing short summaries regarding subjects which have come to the foreground since 1928, such as agranulocytic angina, hyperparathyroidism, psittacosis and spontaneous subarachnoid hemorrhage. No doubt a manual of this sort has a function, what was said of the fourth edition in 1897 describes adequately the thirteenth edition of 1934.

**The Laboratory Notebook Method in Teaching Physical Diagnosis and Clinical History Recording** By Logan Clendenning Price, 50 cents Pp 71 St. Louis C. V. Mosby Company, 1934

In essence this is a notebook with headings dealing with the various points in physical diagnosis which the student can fill out as he examines the patient. The object is to fix in the mind of the student what he actually sees, learns and feels by making an accurate record. The idea seems a good one.

**The Spastic Child** By Marguerite K. Fischel Price, \$1.50 Pp 97 St. Louis C. V. Mosby Company, 1934

This book is a record of rehabilitation—"successfully achieved muscle control"—of patients with Little's disease, written from a somewhat sentimental point of view.

## FURTHER STUDY OF TUBERCULOSIS AMONG MEDICAL AND OTHER UNIVERSITY STUDENTS

OCCURRENCE AND DEVELOPMENT OF LESIONS DURING THE  
MEDICAL COURSE

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### REVIEW OF THE LITERATURE

A study<sup>1</sup> to determine the incidence of tuberculous infections in medical and other university students has been continued. Our objects were to test our former results by more extended observations, to ascertain the time of onset of new lesions and to determine whether those previously found were progressive. We hoped also to obtain some light on the cause or causes of the remarkable frequency of tuberculous disease among medical students.

During the past few years several interesting reports concerning pulmonary tuberculosis among medical students have been published. Fitz<sup>2</sup> stated that among 424 students at Harvard University who were given a roentgenologic examination as part of a general physical examination only 1 case of tuberculosis was discovered. He described certain cases in medical students that are similar to instances of the disease that we have observed among medical students in Philadelphia. Soper and Wilson<sup>3</sup> have studied the incidence of tuberculous lesions in students entering Yale University. The number of medical students is small, but it is of interest that the incidence of tuberculous lesions in students entering the medical school is higher than that in students preparing for professions other than medicine.

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From the Henry Phipps Institute of the University of Pennsylvania

1 Hetherington, H W, McPhedran, F M, Landis, H R M, and Opie, E L. Tuberculosis in Medical and College Students, *Arch Int Med* **48** 734 (Nov, pt 1) 1931

2 Fitz, R. Problem of Pulmonary Tuberculosis in Medical Students, *Tr A Am Physicians* **46** 241, 1931

3 Soper, W B, and Wilson, J L. Detection of Pulmonary Tuberculosis in Three Thousand Students Entering Yale University, *Am Rev Tuberc* **26** 548 (Nov) 1932

Herman, Baetjer and Doull<sup>4</sup> reported a survey of medical students at the Johns Hopkins University School of Medicine from Oct 1, 1926, to Sept 30, 1931. During this time pulmonary tuberculosis (including pleurisy with effusion) developed in 10 students. The average enrolment was 250, suggesting that approximately 60 students graduated each year. Since an average of 2 cases of tuberculosis occurred each year, the results indicate that about 1 in 30, or 3.3 per cent, of the Johns Hopkins medical students acquired pulmonary tuberculosis during their medical course. It is noteworthy that none of the students had died at the time the report was made.

Similarly, at the Western Reserve School of Medicine, with an average enrolment of 250 students, 11 instances of clinical tuberculosis occurred in eight years, as reported by Herman, Baetjer and Doull. If it is assumed that an average of 60 students a year, or a total of 480 students, graduated during this period, the incidence of pulmonary tuberculosis would be 2.3 per cent, that is, of each 1,000 students passing through the medical school, 23 acquired tuberculosis.

At the University of Michigan in 6,755 student years 19 instances of clinical tuberculosis appeared among medical students<sup>4</sup>. If we assume that each student attended the Medical School for four student years, 1,688 students graduated during the years from 1917-1918 to 1930-1931, during which time 19, or 1.1 per cent, acquired pulmonary tuberculosis. Presumably students with tuberculosis which became manifest clinically during the summer vacation were not included.

## INVESTIGATION OF TUBERCULOSIS AMONG VARIOUS STUDENTS

### GRADUATES OF MEDICAL SCHOOLS

Inquiry was made to determine how many cases of tuberculosis have occurred in members of classes that graduated from the medical school of the University of Pennsylvania in the three years preceding the beginning of the present study, and the information given in table 1 was obtained.

Trustworthy information concerning all these cases was obtainable in all save 3 instances through letters from the graduates who had had the disease. Statements from classmates concerning tuberculosis in 3 other members of these classes were not confirmed by satisfactory evidence. It is improbable that the list contains the names of all those who had tuberculosis.

The onset of symptoms in 5 of the students enumerated was in the third year of the medical course, in 4, in the fourth year, and in 5,

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<sup>4</sup> Herman, N. B., Baetjer, F. H., and Doull, J. A. *Bull. Johns Hopkins Hosp.* **51**: 41 (July) 1932.

within one or two years after graduation. One had died, 6 still suffered with the disease, and 5 were in good health, no information about the health of 2 could be obtained.

During the four years from 1929 to 1933, 521 students who graduated from the medical school of the University of Pennsylvania were given roentgenologic examination, and of these 21, or 4 per cent, were found to have clinical tuberculosis. Thus the incidence of clinical tuberculosis is high when the results of our survey are considered in the same light as those of the surveys aforementioned. However, it is noteworthy that some students had symptoms and signs so trivial that tuberculosis would probably not have been diagnosed, at least not until a later date, if a thorough examination, including the roentgenologic, had not been made. Moreover, the class of 1930, examined in our survey of 1929-1930, as previously reported, had a higher incidence of tuberculosis than the three classes that graduated during our subsequent observations.

TABLE 1—*Incidence of Tuberculosis Among Students of the Medical School of the University of Pennsylvania*

	Onset During Medical Course	Onset After Graduation
Class of 1927	3	3
Class of 1928	4	2
Class of 1929	2	

It should be noted that these figures, as in the surveys made elsewhere, include instances of tuberculous disease acquired previous to the student's entrance to the medical school. Moreover, some men are included who were transferred from other classes, having dropped from their original classes to undergo treatment and having returned to graduate with others.

#### MEDICAL STUDENTS

In the examinations reported here, which were undertaken in 1931, 1932 and 1933, we were able to study the incidence and the progression of the lesions that occurred during the medical course. Within this period approximately 400 students have passed through the medical school. During this time 7 cases of clinical tuberculosis have appeared, and, in addition, 12 instances of advanced latent apical tuberculosis involving the lung both above and below the clavicle. These results indicate that clinical tuberculosis develops in almost 2 per cent of medical students during their medical course and that advanced latent infiltrations that are a serious menace to health develop in 3 per cent.

The majority of the students with clinical and with extensive latent disease were unwilling to discontinue their work, and they completed

their medical training and continued their medical careers with only slight modifications of their daily routine. Progressive tuberculosis has not developed in these men, but that the risk involved is considerable is shown by a minority who continued their work but whose disease progressed and finally required care in a sanatorium. We are of the opinion that many students would have been much safer if they had accepted the treatment recommended.

The significance of tuberculous lesions in medical students based on the results of continued examination after graduation will be discussed in a later paper. An editorial in *The Journal of the American Medical Association*<sup>5</sup> cites the causes of death of physicians concerning whom obituary notices were published in that journal in 1932. Only 68, or slightly more than 2 per cent, of 3,142 physicians were reported to have died of tuberculosis. If these figures represent the entire profession, including those who may have broken down with tuberculosis before beginning or in an early stage of their medical careers, the low mortality from tuberculosis suggests that the lesions found in medical students usually do not progress or at least do not result fatally. Perhaps physicians who have clinical tuberculosis understand better than do other patients the necessity for prolonged treatment and are able to obtain positions where treatment may be continued while they support themselves by doing part time work.

Another factor that may influence favorably the outlook for medical students with tuberculous lesions is the absence of continuous contact with open tuberculosis such as occurs frequently among persons living in family groups. In the case of only 1 of the 29 students who have had progressive tuberculosis while under our observation was there a family history of recent contact with the disease. Another student, originally normal roentgenographically, made a daily surgical dressing during the summer for a boy with far advanced tuberculosis and returned to medical school in the autumn with an extensive latent tuberculous lesion. None of the other students with progressive disease had had known contact with pulmonary tuberculosis other than the casual contacts unavoidable in their work and life in a large eastern city.

The results of the examinations of students at Johns Hopkins and students at the Western Reserve School of Medicine, as well as the examinations of medical students at the Henry Phipps Institute, indicate that 2 per cent or more have clinical tuberculosis during their medical course. Roentgenologic examinations of medical students at the Henry Phipps Institute also showed that an additional 3 per cent have latent disease sufficiently advanced to involve the lung both above and below the clavicle.

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5 Deaths of Physicians Published in 1932, editorial, J A M A 100 820 (March 18) 1933

*Results of the Tuberculin Test in Medical Students*—In the survey made in 1929-1930 we found that the incidence of positive reactions to tuberculin among students in the first year of their medical course was approximately the same as that among college students, that the number of reactions increased in each year of the medical course and that in the fourth year almost 100 per cent gave a positive reaction

Since our first report students in the different years of the medical course have been tested with tuberculin in the academic years 1930-1931, 1931-1932, and 1932-1933. First year students were tested at the beginning of the academic year and more advanced students at the end of the year. Between serial tests in the first and second years approximately eighteen months elapsed, and an interval of one year occurred between tests made in the second, third and fourth years.

TABLE 2—*Results of the Tuberculin Test in Medical Students*

Class	1929 1930			1930 1931			1931 1932			1932 1933		
	Number of Students Tested	Number of Positive Reactions	Percentage	Number of Students Tested	Number of Positive Reactions	Percentage	Number of Students Tested	Number of Positive Reactions	Percentage	Number of Students Tested	Number of Positive Reactions	Percentage
1930	111	109	98.2									
1931	126	121	96.0	129	128	99.2						
1932	103	97	94.2	129	125	96.9	134	131	97.2			
1933	99	84	84.8	101	95	94.1	138	136	98.5	138	136	98.5
1934				122	102	83.6	108	99	91.7	134	130	97.0
1935							118	104	88.1	113	102	90.3
1936										132	115	87.1

At the beginning of each year a small number, perhaps 2 or 3 per cent, fail to continue with their respective classes, and at the beginning of the third year a group of students who have taken the first two years of the medical course elsewhere enter the school. This group, which comprises from 10 to 15 per cent of the third year class, with those who do not continue, is responsible for a slight change in the membership of the classes as they advance from year to year. We do not believe that the change alters our results significantly.

The results of these tuberculin tests with those already reported are shown in table 2 and in a condensed form in table 3.

An increase in the percentage of reactors from approximately 85 per cent of students beginning their first year to 98 per cent or more of graduating students is shown. This increase is numerically most conspicuous at the end of the second year, such a high percentage of third year students react that the increase in the fourth year appears slight.

During the period of our observation, 471 medical students were tested in their freshman year, and of this number 405, or 85.9 per cent, reacted, 425 were tested in their sophomore year, and 393, or 92.5 per cent, reacted, 527 were tested in their junior year, and 512, or 97.1 per cent, reacted, 512 were tested in their senior year, and 504, or 98.4 per cent reacted. Concurrently with the steadily increasing incidence of infection shown by the tuberculin test, an increasing number of tuberculous infiltrations were discovered by roentgenograms, although no other correlation could be found between the incidence or severity of sensitivity to tuberculin and the incidence or course of demonstrable lesions (p. 719).

Soper and Wilson<sup>3</sup> gave the intracutaneous tuberculin test, using 1 mg. of old tuberculin, to medical students at Yale University in 1931. Of 52 first year students, 40, or 76.9 per cent, reacted, whereas 112, or 94.1 per cent, of students in three upper classes reacted. Herman and his co-workers<sup>4</sup> used 0.1 mg. of old tuberculin intracutaneously

TABLE 3—*Percentage of Positive Reactions to Tuberculin in Medical Students*

Class	First Year	Second Year	Third Year	Fourth Year
1930				98.2
1931			96.0	99.2
1932		94.2	96.9	97.2
1933	84.8	94.1	93.5	98.5
1934	83.6	91.7	97.0	
1935	88.1	90.3		
1936	87.1			

in a test of medical students at Johns Hopkins University in 1929-1930. The incidence of positive reactors was 56.9 per cent in the first year class, 77.9 per cent in the second year class, 93.5 per cent in the third year class and 91.5 per cent in the fourth year class. Doubtless a somewhat higher percentage would have reacted if 1 mg. had been used. These results, as well as our own, suggest that the frequency of tuberculous infection is high among medical students. The results of tuberculin tests of third and fourth year dental students and of fourth year law students at the University of Pennsylvania, reported on later in the article, are also high and suggest that the opportunities for infection of university students in a large eastern city are sufficiently numerous to cause positive reactions in almost all after several years' residence. Accordingly, no conclusions have been reached regarding the relative frequency of opportunity for tuberculous infection in different professional schools.

*Results of Roentgenologic Examination of Medical Students*—An attempt was made to give serial roentgenologic examinations to all medical students during the academic years 1930-1931, 1931-1932 and 1932-1933 in addition to the examinations made in the year 1929-1930.

The results of these examinations for each year are shown in table 3. Each class is designated by the year in which the students graduate, for example, in the academic year 1930-1931 the class of 1934 were first year students, in 1931-1932 they were second year students, etc., the classes maintain their identity throughout the medical course, but the students in them vary somewhat, as has already been explained (p 713).

TABLE 4—Results of Roentgenologic Examinations of Medical Students

Year	Number	Number with Calcified Foci in the Lungs or Tracheo-bronchial Lymph Nodes	Number with Nonapical Tuberculous Pulmonary Infiltration	Number with Supra-clavicular Apical Infiltration	Number with Supra-clavicular and Infra-clavicular Infiltration	Number with Manifest Tuberculosis
Class of 1930						
1929-1930	122	21	1	11	5	9
Class of 1931						
1929-1930	129	21	1	13 (1)	2	4
1930-1931	134	21	1	13	3	(1) 5†
Class of 1932						
1929-1930	103	14	0	13 (2)	1	0
1930-1931	133	19	(1) 0	(2) 15	4	2
1931-1932	133	17	(1) 0	(2) 15*	4	(1) 2
Class of 1933						
1929-1930	98	23	0	10 (4)	1	1
1930-1931	104	26	0	(1) 10 (3)	4	1
1931-1932	139	28	(3) 0	(3) 10	6	4
1932-1933	132	30	(3) 0	(3) 11†	7	4
Class of 1934						
1930-1931	122	11	0	18	1	0
1931-1932	108	10	0	20	1	0
1932-1933	133	19	0	(1) 20†	(1) 3	0
Class of 1935						
1931-1932	119	16	0	10 (1)	4	0
1932-1933	113	21	0	11	4	1
Class of 1936						
1932-1933	132	22	0	11	0	0

\* Two lesions progressed but did not extend below the clavicle

† One lesion progressed but did not extend below the clavicle

‡ One student who dropped from the class with clinical tuberculosis is included. He returned and completed his course in 1932, he is represented by the figure in parentheses

In table 4 the figures in parentheses to the left of the main column represent lesions found in students who entered the class after the first year. There were 13 students with lesions of this sort, in no instance was any change in the lesion noted at a subsequent examination. The figures in parentheses to the right of the main column represent lesions found in students in their first year, which lesions later progressed and as noted after subsequent examinations are listed in another column as more advanced lesions.

As indicated by the asterisks, 4 students had apical lesions that progressed but were limited to the apex of the lung above the clavicle



during the period of our observation Six students whose roentgenograms showed no abnormalities in the freshman year had apical lesions limited to the lung above the clavicle that were demonstrated in later roentgenograms Eight students whose roentgenograms in the freshman year showed supraclavicular lesions had progressive lesions that in later films were situated both above and below the clavicle, and 11 students whose original films showed no abnormalities had lesions situated both above and below the clavicle

Of the students in the group with more advanced lesions, 16, both above and below the clavicle, 7 had clinical and 12 had latent tuberculosis

*Incidence of Progressive Tuberculous Lesions During the Medical Course*—Table 4 is arranged to show the number and extent of the lesions found in each successive academic year in the members of the same class A careful review of roentgen films in each instance has been made in order to determine whether or not there has been progression in cases in which the lesion was present when the student entered the class and to determine as closely as possible the date of onset in instances in which the lesion was not present The figures in parentheses to the left of the main columns represent lesions in students who entered the class during the medical course These lesions are not included in the main column of figures At the right of the main column under "supraclavicular apical infiltrations" the figures in parentheses, also not included in the main column, represent lesions that progressed and in later years were included with the more advanced lesions It should be remembered that the examination of the first year class is made at the beginning of the academic year and that examinations of the other classes are made toward the end of the academic year

By our serial observations we have been able to determine accurately the number of instances of manifest and latent tuberculosis that have appeared or progressed during a period of almost four years The number of cases of new or progressive tuberculosis found represents the incidence of lesions occurring in three medical classes throughout their course The class of 1933 is one of these, having been examined in its first year and reexamined in its second, third and fourth years The class of 1934, which was examined in its first year and reexamined in its second and third years, with the class of 1931, which was first examined in its third year and reexamined in its fourth year, is taken as another Similarly, the class of 1935, examined in its first year and reexamined in its second, with the class of 1933, first examined in its second year and reexamined in its third and fourth years, is the third Since there are approximately 130 students in each class, the number of cases of tuberculosis that develop or progress should represent the number appearing in about 400 students observed throughout their medical course

During the period of our observation, 7 students have had clinical pulmonary tuberculosis, and 12 have had extensive tuberculous infiltration, situated both above and below the clavicle but unaccompanied by symptoms or physical signs. In addition, 6 students have had apical lesions limited to the lung above the clavicle, and 4 others have had progressive disease limited to the lung above the clavicle.

If one assumes that this number of lesions represents the incidence of new or progressive disease occurring in 400 students during their medical course, 1.75 per cent had clinical tuberculosis, 3 per cent, extensive latent apical disease, 1.5 per cent, latent apical tuberculosis limited to the lung above the clavicle, and an additional 1.25 per cent, small apical lesions that increased in extent but not sufficiently to involve the lung below the clavicle. A total of 7.5 per cent of the students had new or progressive tuberculous lesions during their medical course.

A considerable number, approximately 10 per cent, had small apical infiltrations that showed no change during our observation. Another group, representing from 15 to 20 per cent of the students, had calcified foci in the lungs or tracheobronchial lymph nodes, and a few students had more advanced infiltrations, in 1 instance manifest, that have not shown any change.

*Time of Onset or Progression of Lesions*—The 29 cases of tuberculous lesions that progressed during the period of our examinations fall into two groups. On the one hand, 17 have occurred in students examination of whom at the beginning of their medical course failed to reveal any evidence of apical infiltration in roentgenograms. Of the 17 cases in which fresh infiltration developed, 5 were found at the second examination, 9 at the third examination and 3 at the fourth examination. On the other hand, 12 students with progressive disease gave evidence of apical infiltration in the original films. It is by no means certain that the increase in disease was a progression of the infiltration originally seen. In some instances the shadows in the first films were regarded as suspicious only and did not change over a period of eighteen or thirty months, the more extensive infiltration appearing at the third or fourth examination. It is noteworthy, however, that of 6 cases in which the lesion seen at the first examination was unilateral, progression occurred on the same side in 5 instances and on the opposite side in only 1. In 6 instances the original lesion was bilateral. Increase in the area of infiltration was diagnosed at the second examination in 1 case, at the third examination in 7 cases and at the fourth examination in 4 cases.

As regards tuberculosis, the third year of the medical course appears to be most dangerous for the student, for at this time 9 of the 17 cases of new lesions appeared and an increase was first seen in 7 of the 12 cases in which the condition progressed. The first and second years,

included in the interval between the first and second examinations, produced 5 cases of new lesions and 1 case of progression of a lesion, and the fourth year produced 3 cases of new lesions and 4 cases of progression. During his third and fourth years, the student encounters tuberculosis in the hospital wards and the autopsy room. Even though no relation between this exposure and the occurrence of lesions has been established, the greater incidence of development of tuberculous lesions during this time as compared with the first two years suggests the desirability of the utmost precaution in guarding the student against infection. It may also be noted that the third year is the most difficult of the medical course. Steidl<sup>6</sup> analyzed the answers to a questionnaire sent to graduates of the Harvard Medical School. More than half of the students who reported that tuberculosis had developed during their medical course became ill during their third year.

*Incidence of Tuberculous Lesions in Students Entering the Medical School*—Four hundred and seventy-one students were examined in the first year of their medical course. Of this number, 338, or 71.8 per cent, showed no evidence of a tuberculous abnormality on roentgen examination, 72, or 15.3 per cent, had calcified foci in the lungs or tracheobronchial lymph nodes without other demonstrable tuberculous lesions, 61, or 12.9 per cent, had tuberculous lesions at or near the apex. Lesions limited to the apex of the lung above the clavicle occurred in 54 students, and lesions situated both above and below the clavicle occurred in 7 students. We could find no reason for this high incidence of apical tuberculous lesions in students entering the medical school.

*Incidence of Tuberculous Lesions in Students of the Graduating Classes*—In the graduating classes, we found that the incidence of apical lesions, grouped together, was 25, or 20.5 per cent, in 1930, 21, or 15.7 per cent, in 1931, 24, or 18 per cent, in 1932, and 25, or 18.8 per cent, in 1933. When only the more advanced apical lesions are considered, it is found that manifest tuberculosis or latent apical lesions situated both above and below the clavicle occurred in 14, or 11.5 per cent, of students who graduated in 1930, in 8, or 6 per cent, of students who graduated in 1931, in 7, or 5.3 per cent, of students who graduated in 1932, and in 11, or 8.3 per cent, of students who graduated in 1933.

The decreased incidence of the more extensive lesions in students of the graduating classes during the three later years may be due to one or several factors. We believe that our advice regarding prophylactic care given to students with small lesions may have prevented progression

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6 Steidl, J. Tuberculosis Among Medical Students, *Am Rev Tuberc* 26:98 (July) 1932.

of the lesion, at least in some instances. Moreover, after the results of our first survey were reported, it is very unlikely that any student with tuberculosis whose sputum contained tubercle bacilli lived in contact with other students, for the possibility of contagion was recognized by the students, and those whose sputum contained tubercle bacilli were quickly placed under treatment. Although we believe that these factors may have played a part in preventing the development of extensive lesions during the years 1931, 1932 and 1933, it is also recognized that the graduating class of 1930 probably exhibited an unusually high incidence of extensive lesions.

*Attempt to Correlate the Results of the Tuberculin Test and Those of the Roentgen Examination*—We have found no correlation between the results of the tuberculin test and those of the roentgen examination. Approximately 15 per cent of the first year students failed to react to 1 mg of old tuberculin, and 2 students from this group later had latent lesions that were situated both above and below the clavicle. At the time that these lesions were demonstrated roentgenologically both students reacted to 0.01 mg of old tuberculin, there was nothing unusual about the extent or the course of the lesion in either patient. Fifteen tuberculous lesions developed in students who reacted to tuberculin at their first examination. The intensity of the original reaction varied from ++ to 0.01 mg of tuberculin to + to 1 mg and appears to have had no definable influence on the extent or character of the lesion that subsequently developed. The results in this small group do not indicate that there is a significant variation between the students giving a negative reaction to tuberculin and those giving a positive reaction in their liability to the development of tuberculous lesions.

Ten of the 11 students with progressive disease reacted to tuberculin at the time that the lesion was first demonstrated in roentgen films. Six reacted to 0.01 mg, 2 to 0.1 mg, and 2 to 1 mg. One student with a supraclavicular infiltration did not react to 1 mg of old tuberculin, but later, when an increase in the extent of the lesion was demonstrated, he reacted to 1 mg. The severity of the reaction to tuberculin has not been of value in selecting the lesions that progressed.

*Tuberculosis with Sputum Containing Bacilli*—Of the 7 students with clinical tuberculosis, 2 had sputum containing tubercle bacilli, 2 had sputum that failed to show tubercle bacilli and 3 raised little sputum. One student in the class of 1931 with a progressive latent lesion had tubercle bacilli in the sputum a few months after graduation, and 2 other students in the same class who had latent lesions that remained unprogressive during their fourth year have since had tubercle bacilli in the sputum.

## DENTAL STUDENTS

A number of dental students were examined in 1930-1931 to determine the incidence of tuberculous infection and tuberculous lesions among them. Table 5 shows the results of the tuberculin tests, and table 6 the results of roentgenologic examinations presented in a manner similar to that used in the tables for medical students.

The number of dental students reacting to tuberculin, shown in table 5 is high. In the third year 88 per cent of 83 students reacted, and in the fourth year, 100 per cent of 45 students. This result suggests that there is as much opportunity for acquiring tuberculous infec-

TABLE 5—Results of the Tuberculin Test in Dental Students

Year	Number Tested	Number of Positive Reactions	Percentage of Positive Reactions
Third	83	73	88.0
Fourth	45	45	100.0
Total	128	118	92.1

TABLE 6—Results of Roentgenologic Examinations of Dental Students

Year	Number	Number with Calcified Foci in the Lungs or Tracheo-bronchial Lymph Nodes	Number with Nonapical Tuberculous Pulmonary Infiltration	Number with Supra-clavicular Apical Infiltration	Number with Supra-clavicular and Infra-clavicular Infiltration	Number with Manifest Tuberculosis
Third	83	5	1	9	0	0
Fourth	45	9	0	2	1	0
Total	128	14	1	11	1	0

tion in the dental as in the medical school. On the other hand, only 1 or 0.8 per cent of the 128 students had an advanced apical infiltration that is, situated above and below the clavicle, and 11, or 8.6 per cent had an apical infiltration limited to the lung above the clavicle. A comparison indicates that the incidence of apical lesions is approximately twice as high in medical students and that the more extensive infiltrations occur much less frequently in dental than in medical students, however, the number of dental students is small.

## LAW STUDENTS

A number of students in the final year of the law school were examined. These students were of approximately the same age as the graduating medical students, the majority being 23, 24 and 25 years old. Seventy-two were tested with tuberculin and 70 or 97.2 per cent,

reacted Eighty-three students were given roentgenologic examinations Three, or 3.6 per cent, had calcified foci of the lungs or tracheobronchial lymph nodes, 1, or 1.2 per cent, had latent nonapical tuberculous lesions of the lung, and 4, or 4.8 per cent, had apical lesions limited to the apex of the lung above the clavicle A more advanced infiltration occurred in 2 patients (2.4 per cent) One of these had moderately advanced tuberculosis, and the other had apical disease, extending below the clavicle, which became manifest clinically within a few months of graduation The percentage of law students who reacted to tuberculin is almost as high as the percentage of medical students who reacted However, the results of this limited number of examinations suggest that the incidence of apical disease is decidedly less in law students than in medical students They also suggest that the occurrence of serious disease is by no means rare among law students

#### THE CAUSE OF THE HIGHER INCIDENCE OF TUBERCULOUS INFECTION IN MEDICAL STUDENTS

The observations reported have shown that tuberculosis was more frequent and much more severe in the medical students than in the law students or the dental students examined In first year medical students the incidence of tuberculous lesions at or near the apex of the lung recognizable by roentgenographic examination has been more than 12 per cent Almost all of these lesions have involved only a small amount of pulmonary tissue, and very few have changed during the period of our observation (table 4) In the second year the incidence of apical lesions has increased slightly The greatest change is between the second and the third year, and in the third and fourth years a considerable number of students have had clinically manifest tuberculosis Several possible explanations of the high incidence of tuberculosis in medical students suggest themselves

It is doubtful whether the intensive work demanded of them, with the often continuous sequence of lectures and laboratory periods during the working day, affords an adequate explanation The burden of work that medical students carry is doubtless considerable but does not satisfactorily account for impaired health

Since a large part of the medical students lived in fraternity houses, it was thought possible that living conditions might explain the transmission of infection Visits to the living quarters in these houses, however, revealed no crowding or other condition that could be regarded as favorable to the development of the disease The residents of each house were listed and roommates were identified, but no evidence that the disease occurred in foci or was transmitted by contact within the fraternity houses could be obtained

Medical students are first exposed to possible contact with tuberculosis during the second year of the medical course, when they study gross pathology in the autopsy room and in the pathologic laboratory. Later, during the third and fourth years, they for the first time have contact with patients with tuberculosis in the general and special dispensaries for tuberculosis, in the general hospital and in the special hospitals for tuberculosis.

Observations made at the Henry Phipps Institute by Mrs A E Augustine have shown that the dust in the homes of persons suffering from open pulmonary tuberculosis not infrequently contains viable tubercle bacilli demonstrable by inoculation<sup>7</sup> of guinea-pigs. The presence of tubercle bacilli in dust is presumably a crude index of the danger to which persons in these households are subjected. Mrs C D Gallagher has used a similar method to determine whether tubercle bacilli are demonstrable in the dust of class rooms, autopsy rooms, dispensary rooms and hospital wards where students might come in contact with tubercle bacilli.

Dust collected on sterile filter paper with a sterile camel's hair paint-brush from the surfaces of tables, chairs and other furniture or from the floor was transferred to a wide test tube, from which it was sifted through no 10 silk bolting-cloth into a second smaller test tube temporarily attached to the first by a rubber stopper.

Of the filtered dust, 0.5 Gm was weighed out and mixed with 5 cc of sterile physiologic solution of sodium chloride, 2 cc of this suspension was transferred to each of two test tubes. To one tube was added 4 cc of sterile saline solution, and two guinea-pigs were inoculated subcutaneously, each with 3 cc of this suspension. To the second tube containing 2 cc of the original material was added 2 cc of 3 per cent sodium hydroxide. The mixture was thoroughly shaken and incubated at 37 C for thirty minutes. After incubation it was neutralized with 6 per cent hydrochloric acid, and the volume was made up to 6 cc by the addition of a physiologic solution of sodium chloride. Two guinea-pigs were inoculated subcutaneously, each with 3 cc of the treated dust suspension. Ninety days after the injection of the dust the guinea-pigs were killed.

Table 7 shows the frequency with which dust from various sources contained tubercle bacilli fatal to guinea-pigs.

No tubercle bacilli were found in the dust collected in the amphitheater where many of the lectures to students are given, and none were obtained from the students' laboratory of pathology, but in dust collected from one of the tables in an adjacent room used for demonstrations in gross pathology tubercle bacilli were found. The number of tubercle bacilli was evidently small, since tuberculosis developed in only 1 of the 20 animals inoculated with this dust. Examination of the dust from three rooms where students attend autopsies was made,

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<sup>7</sup> Augustine, A E. Transfer of Tuberculosis by Dust and Other Agents, *J Prev Med* 3:121 (March) 1929.

and in 1 instance tubercle bacilli were found in dust collected at the base of an autopsy table. Dust from three wards in which tuberculous patients are treated was examined. One of the wards was in a new, well equipped building for women with tuberculosis, no tubercle bacilli were found. Two wards for men were in an old building that has recently been abandoned and replaced. In both of these wards tubercle bacilli were found in all save one of five specimens of dust collected from the floors, dust collected from the surface of the furniture in these wards has not produced tuberculosis in guinea-pigs. Dust collected from two examining rooms in the dispensary of the Henry Phipps Institute, where students are taught physical diagnosis of pulmonary tuberculosis, contained no tubercle bacilli.

TABLE 7—*Results of Inoculation of Guinea-Pigs with Dust from Rooms Frequented by Medical Students*

	Untreated Dust		Dust Treated with Sodium Hydroxide	
	Number of Guinea Pigs	Number That Died with Tuberculosis	Number of Guinea-Pigs	Number That Died with Tuberculosis
Students' amphitheater for lectures	4		4	
Students' laboratory of pathology	10		10	
Demonstration room for gross pathology	10		10	1
Autopsy room (Pennsylvania Hospital)	6		6	
Autopsy room (University Hospital)	6		6	
Autopsy room (Philadelphia General Hosp.)	6	1	6	
Men's tuberculosis ward 1, Philadelphia General Hospital	8	2	5	
Men's tuberculosis ward 2, Philadelphia General Hospital	6	1	6	1
Women's tuberculosis ward, Philadelphia General Hospital	4		4	
Examining room for white tuberculous patients, Henry Phipps Institute	2		2	
Examining room for Negro tuberculous patients, Henry Phipps Institute	2		2	

### SUMMARY

The incidence of positive reactions to tuberculin among medical, dental and law students is high. In the graduating classes it approximates 100 per cent.

The incidence of tuberculous lesions at the apex of the lung, demonstrated in roentgen films, was from 15 to 20 per cent in four graduating medical classes, including, in all, 521 students.

The more advanced infiltrations, situated both above and below the clavicle and sometimes producing symptoms or physical signs, occurred in 11.5 per cent of the graduating medical class of 1930, in 6 per cent of the class of 1931, in 5.3 per cent of the class of 1932 and in 8.3 per cent of the class of 1933. Corresponding figures for graduating dental and law students were 2.2 per cent and 2.4 per cent, respectively.



The decreased incidence of more advanced lesions among medical students in the three later years may have been due, in part at least, to suitable prophylactic care taken by the students with small lesions. Moreover, after our first examination contact among the students with persons whose sputum contained tubercle bacilli was presumably ruled out.

After an interval of eighteen months following a first examination three annual reexaminations were made in order to observe the progress of lesions and the incidence of new lesions that occurred during the medical course. Four hundred men were thus reexamined, comprising the equivalent of three classes observed throughout their four years' work. More frequent examinations of individual students were made when indicated.

Under the conditions of our survey, in 17 students the first examination of whom revealed no abnormalities apical infiltration that was considered tuberculous developed, and 12 students who had apical infiltration at the first examination showed progression of their disease. Within this period of observation 1.75 per cent of students had clinical tuberculosis, 3 per cent had advanced latent lesions occupying the apex of one or both lungs, both above and below the clavicle, 1.5 per cent had apical lesions limited to the lung above the clavicle, and 1.25 showed a slight progression in apical lesions limited to the lung above the clavicle. A total of 7.5 per cent of medical students had new lesions or showed progression in old lesions during their medical course.

Small lesions frequently, and more advanced lesions less frequently, found in students when they entered the medical school persisted unchanged throughout the medical course.

The occurrence of new lesions and the progression of old lesions were more frequent in the third year of the medical course than in the other three years combined.

Observations recorded in this paper show that medical students come into contact with tubercle bacilli under conditions that expose them to danger of infection, but it is uncertain whether this exposure actually produces latent or manifest disease. Nevertheless, the facts show the desirability of extreme care to prevent contamination of student work rooms with tubercle bacilli.

Comparison of the incidence of tuberculous lesions in a small number of dental and law students with those in the medical students shows that apical disease was about twice as frequent in the medical students and that the more advanced apical lesions occurred much more frequently among them.

EXAMINATION AND REEXAMINATION OF UNIVERSITY  
STUDENTS DURING THEIR MEDICAL COURSE

*Method*—The tuberculin test consisted of intracutaneous injections of 0.01, 0.1 and 1 mg of standardized old tuberculin. Roentgen examination was made with stereoscopic films in the anteroposterior position, with additional views in other positions when indicated.

In the protocols given later the levels of the ribs and interspaces mentioned in describing the extent of the lesions refer to the posterior aspect of the thorax unless otherwise stated. The weight of the student is expressed as a percentage of the normal weight for sex, age and height. The age given is the age of the student at his first examination.

The diagrams in figure 1 show the extent of the lesions appearing on reexamination in 17 students whose lungs had appeared normal in roentgen films at their first examination. The diagrams in figure 2 show the extent of progressive lesions in 12 students at the first examination and at a reexamination.

## CLASS OF 1931

**CASE 1**—An American man, aged 24, was first examined in April 1930. The weight was 101 per cent. The reaction to 0.01 mg of old tuberculin was ++. Roentgen examination was considered to show no abnormalities. There was no known contact with tuberculosis.

Reexamination in April 1931 revealed a slight irregular shadow in the second interspace on the right, suggesting a thickened pleura. On the left there were shadows in the form of salients projecting into the pulmonary field below the second rib. There was a moderately dense infiltration consisting of spots and strands between the anterior levels of the second and fourth ribs. Physical examination showed restricted movement and diminished resonance over the left apex.

The diagnosis was minimal pulmonary tuberculosis.

**CASE 2**—An American man, aged 23, was first examined in April 1930. The weight was 95 per cent. The reaction to 0.01 mg of old tuberculin was +. Roentgen examination of the lungs showed a scanty infiltration above the clavicle on the right side.

The diagnosis was latent apical tuberculosis.

Reexamination in April 1931 revealed infiltration consisting of soft spots and strands above the clavicle on the right side and above and below the clavicle on the left side.

The diagnosis was progressive latent tuberculosis.

Tubercle bacilli were found in the sputum a few months after graduation.

## CLASS OF 1932

**CASE 3**—An American man, aged 26, was first examined in February 1930. The weight was 81 per cent. The reaction to 0.01 mg of old tuberculin was +. Roentgen examination was considered to show no abnormalities. There was no known contact with tuberculosis.

Reexamination was made in April 1931. The student said that for several days in March 1931 on breathing he had a sharp pain in the right side of the chest. Roentgen examination revealed an area of moderately dense infiltration, consisting of confluent spots, at the anterior level of the third interspace and the fourth rib and interspace toward the axilla on the right side. In the left

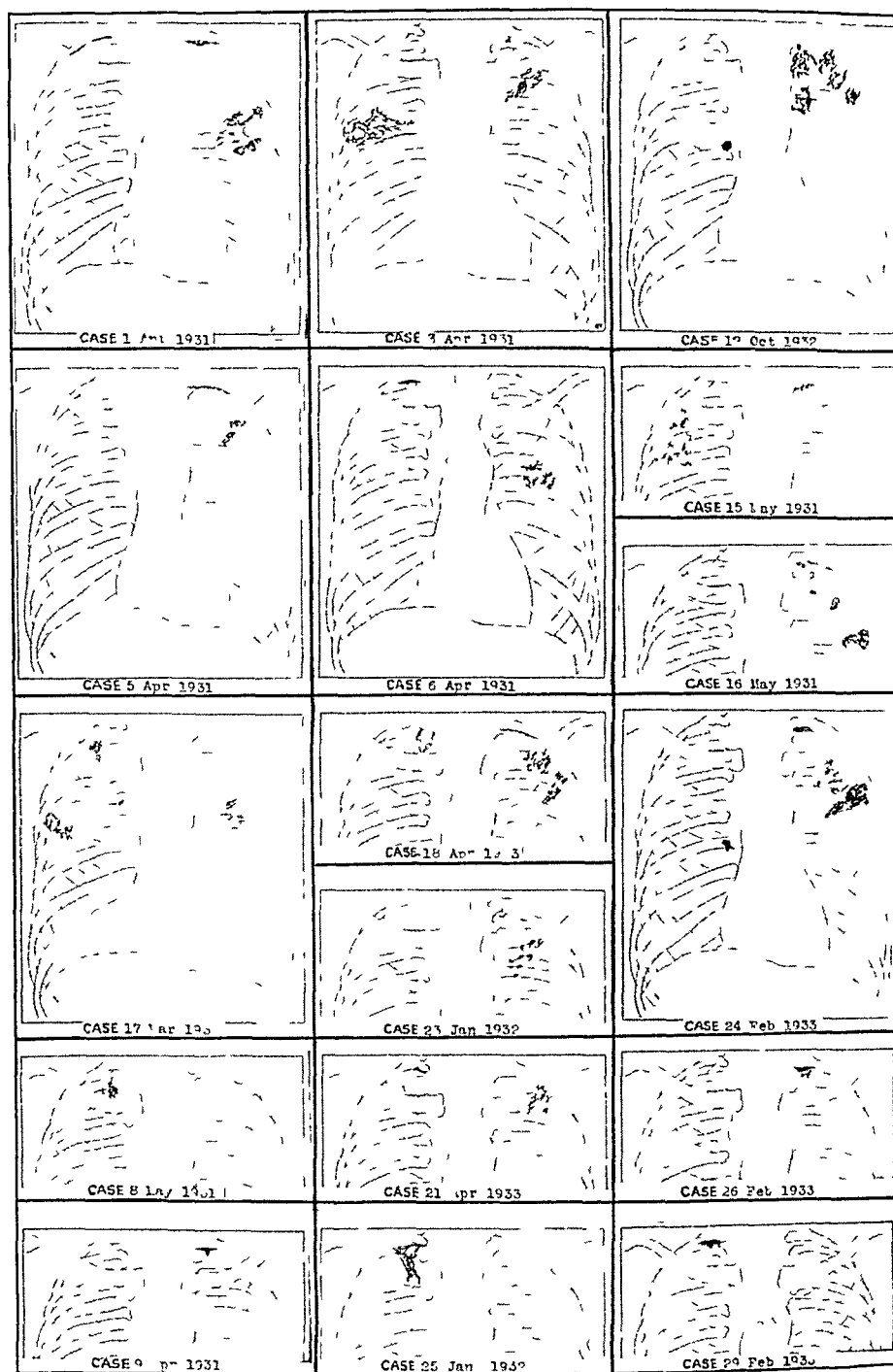
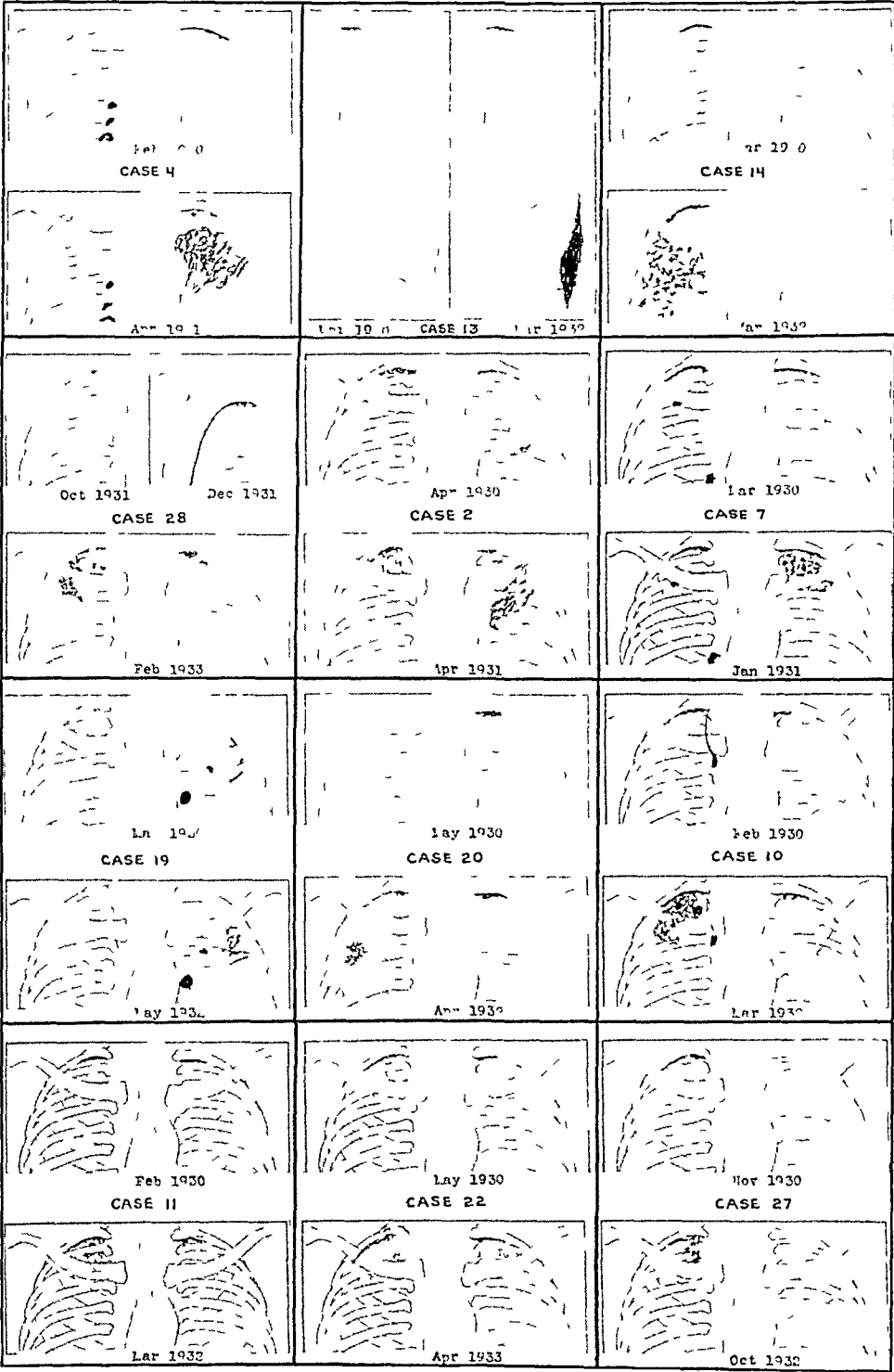


Fig 1—Diagrams showing the extent of the lesions appearing on reexamination in 17 students whose lungs had appeared normal in roentgenograms at their first examination



lung there were scanty spots of infiltration in the second posterior interspace and moderately dense soft spots at the anterior level of the first interspace

The diagnosis was minimal pulmonary tuberculosis

The student remained at work under supervision until January 1932, when he had several small hemorrhages and tubercle bacilli were found on examination of the sputum

CASE 4—An American man, aged 24, was first examined in February 1930. The weight was 96 per cent. The reaction to 0.01 mg of old tuberculin was +. There were no physical signs. Roentgen examination showed slight thickening of the pleura at the left apex with slight shadows in the form of salients projecting into the pulmonary field in the second posterior interspace.

The diagnosis was latent apical tuberculosis

Reexamination was made in April 1931. Roentgen examination showed several calcified foci in the lymph nodes at the hilus of the right lung. On the left side there were salients in the second posterior interspace and moderately dense infiltration consisting of soft confluent spots in the third, fourth, fifth and sixth interspaces. There were diminished resonance and diminished expansion with bronchovesicular breath sounds at the apex of the left lung. The temperature during the evening reached from 99 to 99.5 F. The student cleared his throat but had no other symptoms.

The diagnosis was minimal pulmonary tuberculosis

The student gave up plans for work and rested during the summer of 1930. He returned for his senior year still complaining of elevation of temperature and clearing of his throat. At this time the lesion was more strandlike in appearance. Rigid restriction of activities, increased hours of rest and change of diet were advised, and the student was permitted to continue with his senior year. Roentgen examination in November 1931 and in February 1932 showed a definite increase in the extent and density of the lesion. In February the patient complained of a slight cough and blood-streaked sputum as well as slight fever. The sputum did not reveal tubercle bacilli. The patient was admitted to a sanatorium in March 1932.

CASE 5—An American man, aged 26, was first examined in February 1930. The weight was 116 per cent. The reaction to 1 mg of old tuberculin was ++. Roentgen examination of the lungs revealed no abnormalities.

Reexamination was made in April 1931. Roentgen examination showed scanty salients in the second posterior interspace with an infiltration consisting of ill delimited soft spots at the anterior level of the first interspace on the left side. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis

The student was given advice regarding rest, he continued his medical course under supervision.

Reexaminations in March and December 1932 still showed the infiltration in the same area as before. Its appearance still suggested that it was not a stable lesion and that it might progress.

CASE 6—An American man, aged 24, was first examined in February 1930. The weight was 90 per cent. The reaction to 0.01 of old tuberculin was negative. Roentgen examination of the lungs revealed no abnormalities.

At reexamination in April 1931 thickening of the pleura was seen at the right apex with small salients below the second rib. In the left lung, between the posterior levels of the sixth and eighth ribs, there was infiltration consisting of confluent soft spots. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis

This student continued with his medical course. Roentgen examinations in May and September 1931 and March 1932 showed complete clearing of the lesion.

on the left side. In films taken in June 1932 and January 1933 the apical lesion on the right persisted unchanged.

CASE 7—An American man, aged 23, was first examined in March 1930. The weight was 100 per cent. The reaction to 0.01 mg of old tuberculin was +. Roentgen examination showed thickening of the pleura at the apex of the right lung with densities shaped like salients projecting into the pulmonary field in the second posterior interspace. In addition, there were two peripheral nodules and four calcified areas at the hilus of the right lung. There was a similar pleural thickening at the apex of the left lung. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

Reexamination of this student in January 1931 showed infiltration consisting of moderately dense soft spots at the second and third interspaces above the clavicle and in the fourth interspace posteriorly below the clavicle. There were still no physical signs.

The diagnosis was progressive latent apical tuberculosis.

The student was advised to restrict his activities as much as possible consistent with his work.

Reexaminations in March and June 1931 and in April 1932 showed marked clearing of the lesion, although it was not yet wholly strandlike at the last examination.

CASE 8—An American Negro, aged 25, was first examined in February 1930. The weight was 98 per cent. The reaction to 0.1 mg of old tuberculin was +. Roentgen examination of the lungs revealed no abnormalities.

Reexamination in May 1931 revealed an infiltration on the right side consisting of confluent spots above the clavicle in the posterior second and third interspaces. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

Reexaminations in June, September and December 1931, March 1932 and February, May and September 1933 showed a gradual decrease in the extent of the lesion, which became almost wholly strandlike in appearance.

CASE 9—An American man, aged 23, was first examined in February 1930. The weight was 98 per cent. The reaction to 0.1 mg of old tuberculin was +. Roentgen examination of the lungs revealed no abnormalities.

Reexaminations in April 1931 and March 1932 showed slight thickening of the pleura at the left apex with a strandlike infiltration projecting into the lung in the second posterior interspace. There were no symptoms.

The diagnosis was latent apical tuberculosis.

Reexamination in April 1933 showed no change.

CASE 10—An American man, aged 22, was first examined in February 1930. The weight was 88 per cent. The reaction to 0.01 mg of old tuberculin was ++. Roentgen examination showed small salients below the second posterior rib at both apices.

At reexamination in May 1931 there was no definite change. In March 1932 roentgen examination showed, on the right side, in addition to the salients, soft and confluent spots in the second and third posterior interspaces above the clavicle. Films in April and June 1932 showed an increase in the extent and density of this lesion.

The diagnosis was progressive latent apical tuberculosis.

CASE 11—An American Jew, aged 22, was first examined in February 1930. The weight was 85 per cent. The reaction to 0.01 mg of old tuberculin was +. Roentgen examination showed scanty strandlike infiltration at the apices of both lungs.

Reexamination in April 1931 confirmed the previous observations

The diagnosis was latent apical tuberculosis

Reexamination in March 1932 showed thickening of the pleura at the apex of the right lung with strands and spots in the second and third posterior interspaces above the clavicle. There were three small calcified spots near the hilus of the lung. The left side was unchanged. There were no symptoms and no physical signs.

The diagnosis was progressive latent apical tuberculosis

#### CLASS OF 1933

CASE 12—An American man, aged 22, was first examined in December 1931. The weight was 100 per cent. The reaction to 0.1 mg. of old tuberculin was +. Roentgen examination showed a calcified area at the right hilus.

At a reexamination in March 1932 roentgen films showed very slight, indefinite shadows in the second posterior interspace at the left apex. In October there was a moderately dense infiltration consisting of confluent spots as low as the posterior level of the sixth rib. During the summer of 1932 the student had an illness characterized by indigestion, elevation of temperature and cough. He was in bed for two months.

The diagnosis was minimal pulmonary tuberculosis.

The student continued with his medical course, but his lesion gradually increased in density, and in March his sputum contained tubercle bacilli.

CASE 13—An American man, aged 21, was first examined in March 1930. The weight was 96 per cent. The reaction to 0.01 mg. of old tuberculin was +. Roentgen examination showed slight thickening of the pleura at the apex of the right lung with salients in the second posterior interspace and thickening of the pleura and salients at the apex of the left lung.

Reexamination in April 1931 showed no definite change.

The diagnosis was latent apical tuberculosis.

In March 1932 another roentgen examination showed no change in the lesions at the apexes. At the base of the left lung there was a dense shadow obscuring the costophrenic sulcus. This shadow was 2.5 cm. in thickness and appeared to be due to a localized thickening of the pleura. The breath sounds, movement and resonance were diminished at the base of the left lung. The student stated that he had had some pain in this area several months before examination.

The diagnosis was minimal pulmonary tuberculosis.

At reexaminations in April, May, September and November 1932 a decrease was observed in the density at the base of the left lung. In February a painful, fluctuating swelling developed over the sixth and seventh ribs in the axilla. This swelling, 7 cm. in diameter, was situated exactly at the level of the lesion as shown in the roentgen films.

The diagnosis was tuberculous abscess probably with caries of the rib.

CASE 14—An American man, aged 20, was first examined in March 1930. The weight was 101 per cent. The reaction to 0.1 mg. of old tuberculin was +. Roentgen examination showed slight thickening of the pleura at the apex of the right lung with small salients in the second posterior interspace. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

In May 1931 physical and roentgen examinations showed no change. In March 1932 roentgen examination showed the same appearance at the apex of the right lung above the clavicle. In addition, there was moderately dense infiltration made up of confluent spots between the levels of the fourth and eighth ribs.

posteriorly The student said that he had had a slight cough beginning in December 1931, with clearing of the throat The cough gradually increased in severity, and the student consulted a physician, but the disease remained undiagnosed because no physical signs were present The sputum did not contain tubercle bacilli

The diagnosis was moderately advanced pulmonary tuberculosis

The student was confined to bed at home from May to September and completed his college course, restricting his activities as much as possible Symptoms disappeared during the summer of 1932 and the student remained free from symptoms throughout his senior year

CASE 15—An American man, aged 21, was first examined in March 1930 The weight was 98 per cent The reaction to 1 mg of old tuberculin was negative Roentgen examination of the lungs showed no abnormalities

Reexamination was made in May 1931 The reaction to 0.01 mg of old tuberculin was +++ Roentgen examination showed, at the apex of the right lung, a few small spots in the second posterior interspace and somewhat scanty infiltration made up of soft, ill delimited spots at the anterior levels of the first and second interspaces There were no symptoms and no physical signs

The diagnosis was latent apical tuberculosis

Reexaminations in March and April 1932 and April 1933 showed a slight increase in the extent and density of the lesion both above and below the clavicle on the right side and also a few soft spots above the clavicle on the left side

CASE 16—An American man, aged 22, was first examined in March 1930 The weight was 89 per cent The reaction to 10 mg of old tuberculin was negative Roentgen examination of the lungs revealed no abnormalities

Reexamination was made in May 1931 The reaction to 0.01 mg of old tuberculin was + Roentgen examination showed a small area of confluent spots toward the axilla in the fourth posterolateral interspace on the left side There were also a few ill delimited spots just below the clavicle in the mesial portion of the fourth interspace and a few strands at the apex above the clavicle There were no symptoms and no physical signs

The diagnosis was latent apical tuberculosis

Reexaminations in March, April and May 1932 showed an increase in the extent of the lesion above the clavicle and in the third, fourth and fifth interspaces This student submitted to strict rest in bed during the summer of 1932 Roentgen examination in June, July, September and October 1932 and in January and March 1933 showed slight clearing with an increase in the sharpness of the definition of the lesion

CASE 17—An American man, aged 21, was first examined in April 1930 The weight was 99 per cent The reaction to 0.01 mg of old tuberculin was ++ Roentgen examination of the lungs revealed no abnormalities

At a reexamination in May 1931 no abnormality was found In March 1932 roentgen examination showed, in the right lung, at the anterior level of the third interspace toward the axilla, an area of scanty infiltration consisting of ill delimited spots and strands, on the left side, at the anterior level of the second and third interspaces, there was a small area of moderately dense infiltration consisting of confluent spots Reexamination in April 1932 showed a decrease in the density of the lesion in the left lung with a definite increase in the lesion at the anterior level of the third interspace on the right side and, in addition, the appearance of a few spots at the apex of the lung above the clavicle

The diagnosis was latent apical tuberculosis

At a reexamination in June 1932 a decided increase was observed both in the density and in the extent of the lesion at the apex of the right lung The student



rested during the summer of 1932. Reexaminations were made in March and September 1932 and in February, March and May 1933. The lesion did not change in extent during this time, and its roentgen appearances indicated that it was still unstable. The student, however, completed his senior year without the development of symptoms.

CASE 18—An American man, aged 22, was first examined in May 1930. The weight was 95 per cent. The reaction to 0.01 mg of old tuberculin was +. Roentgen examination of the lungs showed no abnormalities.

At a reexamination in April 1931 and in May 1932 no abnormalities were found. In April 1933 roentgen examination showed a small area of ill delimited spots in the mesial half of the apex of the right lung, in the second and third interspaces posteriorly. At the apex of the left lung there were a few scattered spots above the clavicle and moderately dense infiltration consisting of flocculent spots at the anterior levels of the first and second interspaces toward the axilla. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

CASE 19—An American woman, aged 26, was first examined in May 1930. The weight was 79 per cent. The reaction to 1 mg of old tuberculin was +. Roentgen examination showed a calcified nodule and a calcified area at the hilus of the left lung. There were a few scattered strands above the clavicle and at the anterior levels of the second and third interspaces toward the axilla. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

At a reexamination in May 1931 the reaction to 0.01 mg of old tuberculin was ++. Roentgen examination showed no change. In April and May 1932 roentgen examination showed an increase in the infiltration at the anterior levels of the second and third interspaces toward the axilla. There were no symptoms and no physical signs. Reexamination in September 1932 showed that the lesion on the left side was unchanged and that there was, on the right side, at the anterior level of the third interspace, a moderately dense soft spot about 2 cm in diameter. Reexamination in November 1932 and April 1933 showed apparently complete clearing of this spot of infiltration, the infiltration on the left side had also decreased.

CASE 20—An American man, aged 21, was first examined in May 1930. The weight was 90 per cent. The reaction to 1 mg of old tuberculin was +. Roentgen examination showed slight infiltration in the second posterior interspace on the left side. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

At a reexamination in May 1931 no change was found. In March and April 1932 roentgen examination showed, on the right, a small area of infiltration in the second posterior interspace above the clavicle and an area of ill delimited spots measuring 6 by 4 cm at the posterior levels of the fourth and fifth interspaces toward the axilla. At the left apex there was thickening of the pleura with salients projecting into the pulmonary field. There were no symptoms and no physical signs. Reexamination in April 1933 showed slight clearing of the infiltration below the clavicle on the right side. Bilateral infiltration in the second posterior interspace was still present.

CASE 21—An American man, aged 25, was first examined in April 1930. The weight was 91 per cent. The reaction to 1 mg of old tuberculin was +. Roentgen examination of the lungs showed no abnormalities.

At reexaminations in May 1931 and March 1932 no definite abnormality was found. Reexamination was made in April 1933. The reaction to 0.01 mg of

old tuberculin was + + + Roentgen examination showed slight thickening of the pleura in the second posterior interspace on the right and on the left side a small area of ill delimited spots at the posterior level of the first interspace There were no symptoms and no physical signs

The diagnosis was latent apical tuberculosis

CASE 22—An American man, aged 20, was first examined in May 1930 The weight was 94 per cent The reaction to 0.1 mg of old tuberculin was + + Roentgen examination showed very scanty ill delimited spots at the apexes of both lungs and at the second and third posterior interspaces

Reexaminations in May 1931 and March 1932 showed no change In April and May 1933 roentgen examination showed ill delimited spots and strands at the posterior second and third interspaces above the clavicle on both sides

The diagnosis was progressive latent apical tuberculosis

#### CLASS OF 1934

CASE 23—An American man, aged 21, was first examined in November 1930 The reaction to 0.1 mg of old tuberculin was + + + Roentgen examination of the lungs revealed no abnormalities

Reexamination in January 1932 showed infiltration consisting of somewhat scanty spots and strands above and below the clavicle in the second, third and fourth interspaces on the left side There were no symptoms and no physical signs

The diagnosis was latent apical tuberculosis

CASE 24—An American man, aged 21, was first examined in December 1930 The weight was 92 per cent The reaction to 0.01 mg of old tuberculin was + Roentgen examination of the lungs gave negative results

At a reexamination in January 1932 no abnormality was found In February 1933 roentgen examination showed faint, ill delimited spots above the clavicle in the third posterior interspace and below the clavicle in the fifth posterior interspace On the left side there were faint salients in the second posterior interspace and moderately dense flocculent spots at the posterior fourth rib and interspace and a small area of consolidation in the fourth and fifth interspaces toward the axilla There were no symptoms and no physical signs

The diagnosis was latent apical tuberculosis

CASE 25—An American man, aged 20, was first examined in December 1930 The weight was 92 per cent The reaction to 0.1 mg of old tuberculin was + + Roentgen examination of the lungs showed no abnormalities

In January 1932 another roentgen examination showed faint salients and soft spots in the second posterior interspace on the right side There were no symptoms and no physical signs A diagnosis of latent apical tuberculosis was made Reexamination in February 1933 showed moderately dense infiltration consisting of confluent spots above the clavicle in the second and third posterior interspaces

The diagnosis was progressive latent apical tuberculosis

CASE 26—An American man, aged 21, was first examined in November 1930 The weight was 101 per cent The reaction to 0.1 mg of old tuberculin was + + Roentgen examination of the lungs revealed no abnormalities

At a reexamination in January 1932 no abnormality was found In February, March and May 1933 roentgen examination showed thickening of the apical pleura with salients in the second posterior interspace

The diagnosis was latent apical tuberculosis

CASE 27—An American man, aged 22, was first examined in November 1930. The weight was 100 per cent. The reaction to 1 mg of old tuberculin was negative. Roentgen examination of the lungs showed thickening of the apical pleura with slight salients in the second posterior interspace on the right side. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

At a reexamination in January 1932 the reaction to 1 mg of old tuberculin was negative. The roentgen appearance was unchanged. In October 1932 the reaction to 1 mg of old tuberculin was ++, and roentgen examination showed, in addition, moderately dense confluent spots in the second and third posterior interspaces. Reexamination in December 1932 and March and May 1933 showed no definite change.

The diagnosis was latent apical tuberculosis.

#### CLASS OF 1935

CASE 28—A Spanish-American man, aged 21, was first examined in October. The weight was 95 per cent. The reaction to 0.01 mg of old tuberculin was ++++. Roentgen examination showed soft ill delimited spots above the clavicle on the right and salients in the second posterior interspace on the left. There were no symptoms and no physical signs.

The diagnosis was latent apical tuberculosis.

At a reexamination in December 1931 this student gave a history of pain on the right side and shortness of breath of a few days' duration. Roentgen examination showed a pneumothorax on the right side with a small amount of fluid in the costodiaphragmatic sulcus.

The diagnosis was minimal pulmonary tuberculosis and spontaneous pneumothorax.

Reexamination in February 1932 showed absorption of the pneumothorax with no change in the roentgen appearance of the infiltration from that shown at the original examination. In February 1933 roentgen examination showed ill delimited spots in the second, third and fourth interspaces above and below the clavicle on the right side. On the left side there was no change.

The diagnosis was minimal progressive pulmonary tuberculosis.

CASE 29—An American man, aged 22, was first examined in October 1931. The weight was 95 per cent. The reaction to 0.01 mg of old tuberculin was ++. Roentgen examination of the lungs showed no abnormalities.

At a reexamination in February 1933 roentgen examination of the lungs showed thickening of the apical pleura with salients projecting into the pulmonary field in the second posterior interspace on the right side.

The diagnosis was latent apical tuberculosis.

Miss Eleanor S. Cooper of the Henry Phipps Institute gave us editorial assistance.

# DIURESIS FOLLOWING THE ADMINISTRATION OF SALYRGAN

ITS EFFECT ON THE SPECIFIC GRAVITY, THE TOTAL NITROGEN AND  
THE COLLOID OSMOTIC PRESSURE OF THE PLASMA OF NORMAL  
AND OF EDEMATOUS DOGS

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A number of investigators have reported studies of the concentration of plasma proteins at various periods of time following the administration of mercurial diuretics. The purpose of these studies was to establish evidence pointing to a renal or an extrarenal action of the drugs. Saxl and Heilig,<sup>1</sup> Crawford and McIntosh,<sup>2</sup> Bohn,<sup>3</sup> Claussen<sup>4</sup> and Meyer<sup>5</sup> found a drop in plasma protein concentration during the first two hours after the injection of merbaphen or of salyrgan. In some instances this was followed later by a rise in the protein value. Others, notably Nonnenbruch,<sup>6</sup> reported an increase in the protein concentration of the plasma following the administration of mercurial diuretics,

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1 Saxl, P, and Heilig, R. Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjectionen, *Wien klin Wchnschr* **33** 943, 1920, Ueber die Novasuroidiurese, *Ztschr f d ges exper Med* **38** 94, 1923

2 Crawford, J H, and McIntosh, J F. Observations on the Use of Novasurol in Edema Due to Heart Failure, *J Clin Investigation* **1** 333, 1925

3 Bohn, H. Experimentelle Studien uber die diuretische Wirkung des Novasurols, *Ztschr f d ges exper Med* **31** 303, 1923, Fortgesetzte Studien uber Novasurol, seine Wirkung bei verschiedenen Lebensaltern und bei Diabetikern, sowie sein etwaiger Einfluss auf Ionenverschiebungen im Organismus, *Deutsches Arch f klin Med* **143** 225, 1923

4 Claussen, F. Ueber die Diurese der Herzkranken, *Ergebn d inn Med u Kinderh* **43** 764, 1932

5 Meyer, P. Untersuchungen uber den kolloidosmotischen Druck des Blutes. II Die Salyrgandiurese, *Ztschr f klin Med* **116** 174, 1931

6 Nonnenbruch, W. Ueber die Wirkung des Novasurols auf Blut und Diurese, *Munchen med Wchnschr* **68** 1282, 1921

whereas Bleyer<sup>7</sup> found no constant changes Meyer<sup>5</sup> and Kylin<sup>8</sup> observed a fall in the colloid osmotic pressure during the first hour after the administration of salyrgan, which they interpreted as evidence of an extrarenal action of the drug Oelkers,<sup>9</sup> on the other hand, found a significant rise in the colloid osmotic pressure in patients from two to four hours after the administration of salyrgan The conflicting results of these studies are due in part to the drawing of deductions from slight changes<sup>10</sup> and also to the differences in the time at which observations were made<sup>11</sup> In a recent, carefully controlled study on dogs, Schmitz<sup>12</sup> measured the refractive index of plasma every three minutes after the administration of salyrgan until the onset of diuresis without finding any evidence of hydremia His charts showed, however, an increase in the refractive index during the course of the diuresis

The purpose of the work reported in the present paper was to measure at hourly intervals the specific gravity and the total nitrogen content and at various times the colloid osmotic pressure of the plasma in dogs following the administration of salyrgan The occurrence of changes indicating a dilution or a concentration of the blood might be expected to affect all of these measurements in the same direction Previous investigators in this field have used in their studies normal dogs, rabbits and human beings and patients with edema The experiments on normal animals were unsatisfactory in most instances because the diuresis provoked by salyrgan is not great unless water is given before or during the experiment In our hands salyrgan alone failed to cause a significant increase in the urinary output of normal dogs that did not receive water during the experiment Thus the flow of urine increased from between 0.1 and 0.3 cc per minute in the control periods to a maximum of only 0.5 cc per minute in experiments in which salyrgan was given If, on the other hand, the animal received water by stomach tube during the experiment, the interpretation of the changes in the blood following the administration of salyrgan was rendered

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7 Bleyer, L Erfahrungen über die Novasuroidiurese, *Klin Wchnschr* **1** 1940, 1922

8 Kylin, E Studien über den kolloidosmotischen (onkotischen) Druck XVIII Ueber die Einwirkung verschiedener Diuretika auf den kolloidosmotischen Druck, *Arch f exper Path u Pharmakol* **164** 33, 1932

9 Oelkers, H A Untersuchungen über den kolloidosmotischen Druck des Serums, *Ztschr f klin Med* **115** 854, 1931

10 Schmitz, H L Studies on the Action of Diuretics I The Effect of Euphyllin and Salyrgan upon Glomerular Filtration and Tubular Reabsorption, *J Clin Investigation* **11** 1075, 1932

11 Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol 1, p 666

12 Schmitz, H L Studies on the Action of Diuretics II The Effect of Salyrgan upon the Water Content of the Plasma as Measured by the Refractive Index, *J Clin Investigation* **12** 741, 1933

difficult by the fact that water administered alone causes a measurable dilution of the blood plasma. Because of these considerations the dogs were rendered edematous by plasmapheresis and the administration of salt and a low protein diet before the diuretic was given. It was found that such dogs responded to salyrgan with marked diuresis, the maximum urinary output usually rising from less than 1 cc to from 7 to 11 cc per minute without the necessity of administering water before or during the experiment. We consider that the brisk diuresis which occurs in such edematous dogs is more likely to cause a measurable change in the plasma concentration than the less marked response of normal dogs to salyrgan. In addition, we believe that edematous dogs are better subjects for this type of observation than edematous patients because of the complicating factor of circulatory or renal disease commonly present in the latter.

#### PROCEDURE

All experiments were performed on female dogs weighing from 15 to 23 Kg. The normal dogs were fed a meat diet. Those made edematous by plasmapheresis received a low protein diet similar to that used by Shelburne and Egloff<sup>13</sup>

*Normal Dogs*—In this group of three dogs seventeen experiments were performed. (1) in some of these the dogs received no water during or for fourteen hours before the observation, and (2) in some water was allowed ad libitum until one hour before the experiment and was administered by stomach tube during the six hours of observation, 66 cc per kilogram of body weight being given each hour. In both groups the urinary volume and the plasma specific gravity following the administration of salyrgan were compared with the values obtained in control experiments (i.e., without salyrgan) on the same dogs.

*Edematous Dogs*—Fourteen experiments were carried out on four dogs while they were edematous. Five of these were control experiments in which no diuretic was given. In the remaining nine, salyrgan was given intravenously. In all observations on edematous dogs no water was given either during or for fourteen hours before the experiment. The dogs received a low protein diet, and the production of edema was further accelerated by the giving of large doses of a 0.9 per cent solution of sodium chloride by stomach tube, usually from 1,500 to 2,000 cc a day. The usual routine of plasmapheresis was to remove from the femoral artery from 400 to 600 cc of blood twice a day, reinjecting the cells suspended in a modified Locke solution. The procedure was carried out under aseptic conditions and was continued until the animal exhibited marked pitting edema of the hindlegs and of the abdominal wall and showed a retention of fluid by a diminished urinary output. Plasmapheresis was omitted for eighteen hours before the experiment. By this time the plasma proteins had reached a relatively constant state, as attested by our results in the control group in which the specific gravity and the total nitrogen content of the plasma showed only sporadic variations during the six hours of observation. Following the experiment, plasmapheresis and the administration of a physiologic solution of sodium chloride were resumed for a period of days until the dog was edematous and in proper condition for another study.

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<sup>13</sup> Shelburne, S. A., and Egloff, W. C. Experimental Edema, Arch. Int. Med. 48: 51 (July) 1931.

Urine was obtained by catheter at varying intervals during the experiments and was recorded on the charts in terms of cubic centimeters per minute at the midpoint of the time-period during which the urine was collected

Salyrgan was administered intravenously at the times recorded on the charts in doses of 0.05 cc per kilogram of normal body weight

Samples of from 5 to 7 cc of blood were withdrawn either from the jugular vein or from a vein of the leg with a minimum of stasis at the times indicated in the charts. The blood was transferred to a centrifuge tube containing 0.05 cc (in later experiments 0.08 cc) of a 3 per cent solution of an anticoagulant from dog liver. The tube was tightly corked and centrifugated for twenty minutes. The plasma specific gravity was determined by the method of Moore and Van Slyke<sup>14</sup>. In the nonedematous dogs only single determinations of specific gravity

*Values for Colloid Osmotic Pressure in Millimeters of Water*

				Time From Start of Experiment, Hours						
Water		Experiment	Animal	Start	1	2	3	4	5	
Normal dogs	None	Control	A 13	263					262	
			A 16	288			283			
			A 14	285			265			
	None	Salyrgan*	A 12	239	235					
			A 14	295		283				
	6.6 cc per kilo gram of body weight per hour	Control	A 11	303				243		
			A 12	254				205		
			A 12	242				211		
	6.6 cc per kilo gram of body weight per hour	Salyrgan†	A 11	280					230	
			A 13	236						207
			A 12	243			235			
	None	Control	A 11		85				90	
A 12			98					93		
A 12			83		80					
Edema tous dogs	None	Salyrgan†	A 11	80			113			
			A 11	71		68				
			A 11		81				109	
			A 12	97		76				
			A 12	82		80				
			A 12	75		73				
			A 15	91		90				
			A 17	113					134	
			A 17	84				111		123

\* Salyrgan administered thirty minutes after the start of the experiment

† Salyrgan administered ninety minutes after the start of the experiment

were made, but in the edematous dogs determinations were made in duplicate. The total nitrogen content was measured in duplicate by the micro-Kjeldahl method, using seventieth-normal acid and alkali. The nonprotein nitrogen value was not determined as a routine, so that the figures, although applicable to a study of the dilution and concentration of blood, cannot be translated accurately into terms of protein. No correction was made for the dilution caused by the solution of the anticoagulant.

Measurements of the colloid osmotic pressure were made by the second method of Krogh and Nakazawa<sup>15</sup> with modifications as suggested by Turner<sup>16</sup>. They

14 Moore, N. S., and Van Slyke, D. D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* 8: 337, 1930.

15 Krogh, A., and Nakazawa, F. Beitrage zur Messung des kolloidosmotischen Druckes in biologischen Flussigkeiten, *Biochem. Ztschr.* 188: 241, 1927.

16 Turner, A. H. The Validity of Determinations of the Colloid Osmotic Pressure of Serum, *J. Biol. Chem.* 96: 487, 1932.

were carried out in duplicate on two samples of plasma at various intervals of time during the experiments. The membranes used were cut from sheets of cellophane no 600. The outer liquid was a 0.9 per cent solution of sodium chloride. Final readings were made after between twenty and twenty-four hours. The level of equilibrium was established by finding the pressure at which the capillary column of fluid remained constant for from ten to fifteen minutes after pressures above and below that point had been ascertained. Gross errors caused by leaks in the osmeters or by bubbles could be detected readily. Because of these, it was not possible to obtain final duplicate readings in all determinations. Duplicate readings

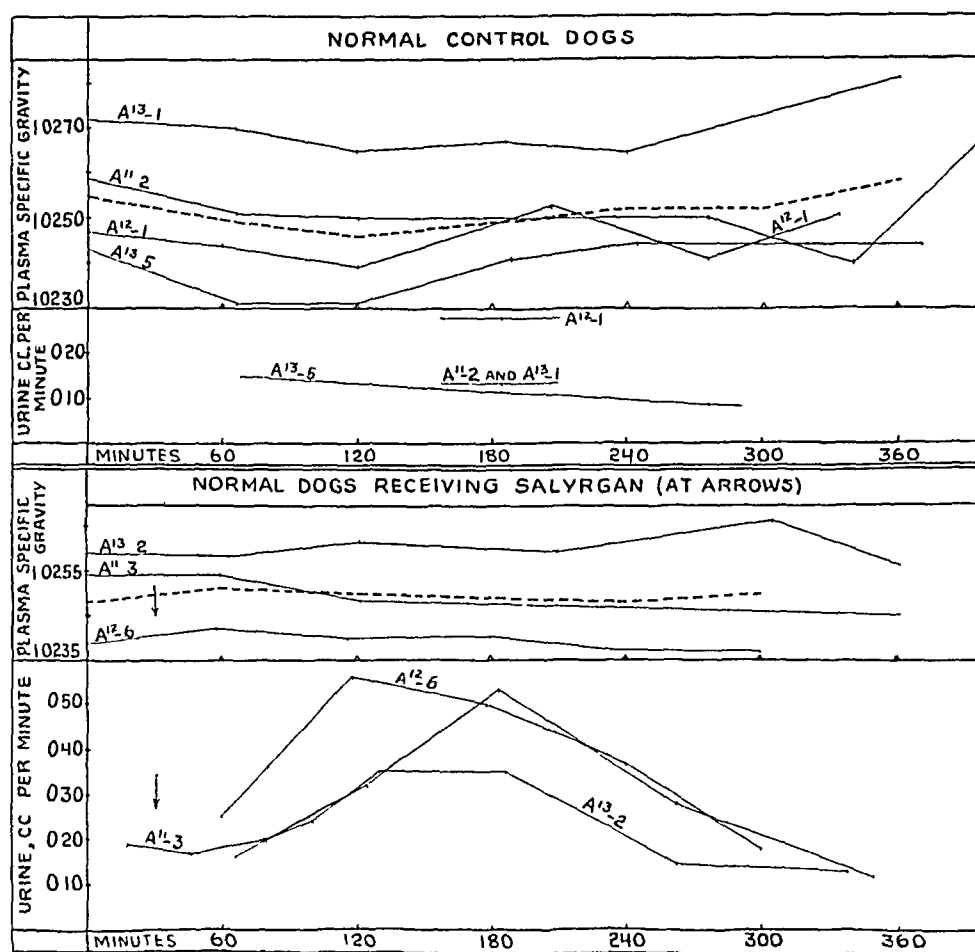


Fig 1—Chart showing the effect of the administration of salyrgan on the volume of the urine and on the specific gravity of the plasma in normal dogs. The dotted lines in figures 1 to 4 represent composite curves.

on normal plasma corresponded with an average difference of 12 mm of water, those on plasma from edematous dogs showed an average variation of 4 mm of water. This degree of agreement is adequate to enable one to detect such gross changes in the colloid osmotic pressure of the plasma as may result from the administration of water or of diuretics.

## RESULTS

The results obtained are shown in figures 1 to 4 and in the table and require little explanation. It may be seen in figure 1 that when water was not given we were unable to obtain significant diuresis follow-



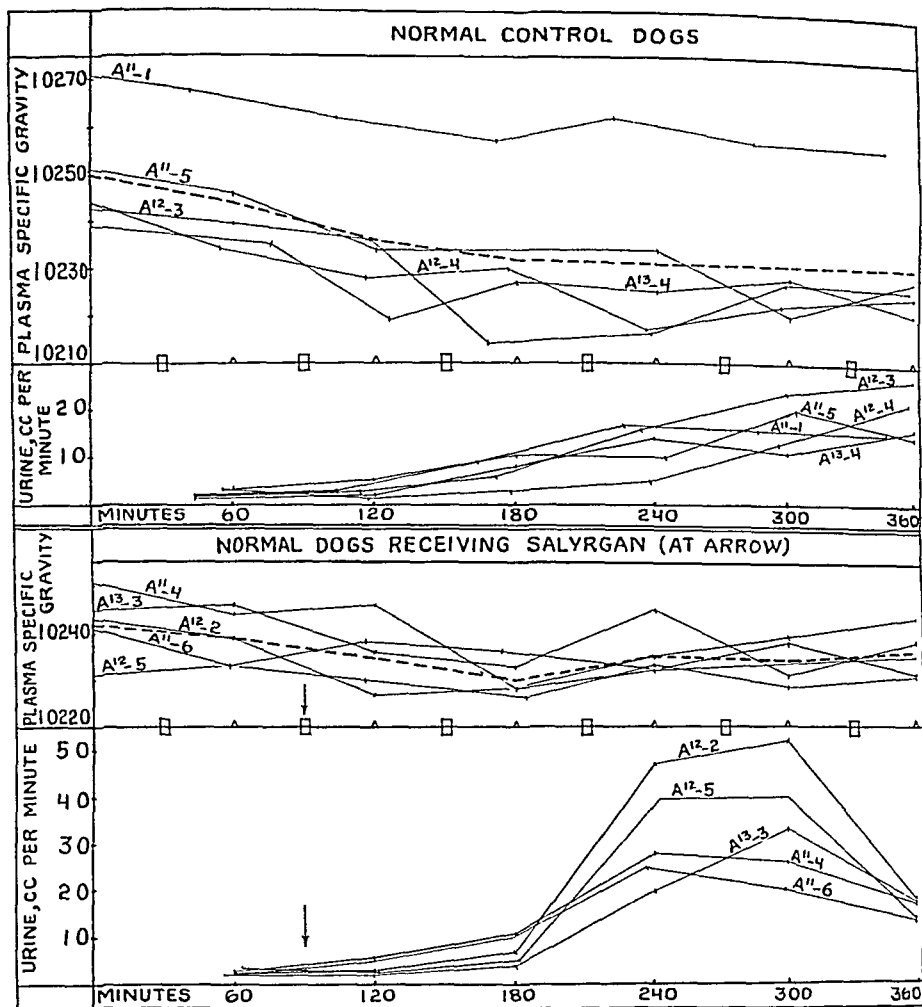


Fig 2—Chart showing the effect of the administration of salyrgan on the volume of the urine and on the specific gravity of the plasma in normal dogs that were given 66 cc of water per kilogram of body weight per hour as indicated by the squares

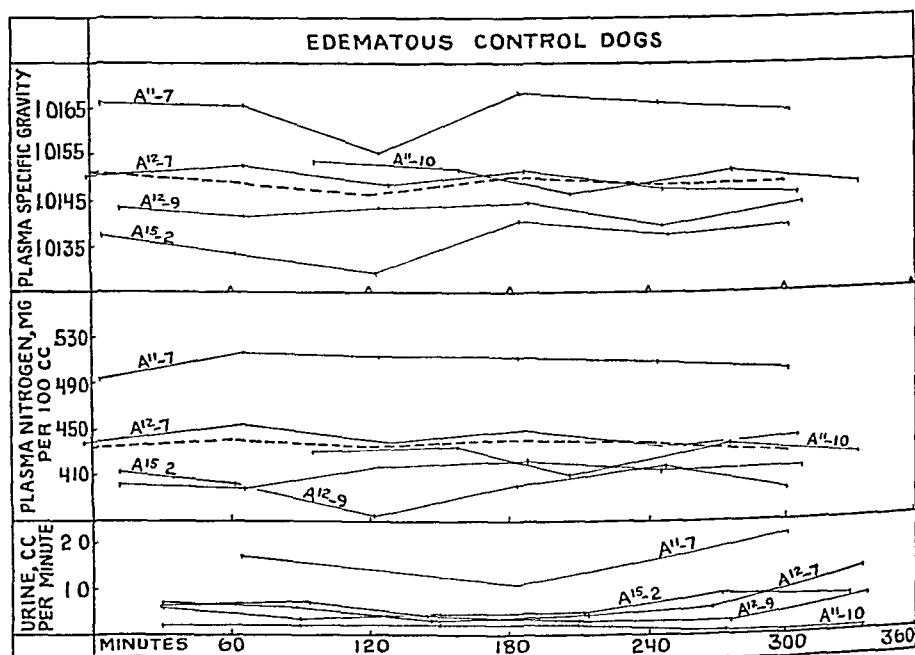


Fig 3—Chart presenting the results in control experiments showing the constancy of the specific gravity and of the total nitrogen content of the plasma during a six hour period in edematous dogs

ing the administration of salyrgan The administration of 66 cc of water per kilogram of body weight per hour (fig 2) caused diuresis and also a constant decrease in the specific gravity of the plasma and of the colloid osmotic pressure (table) In the experiments in which both

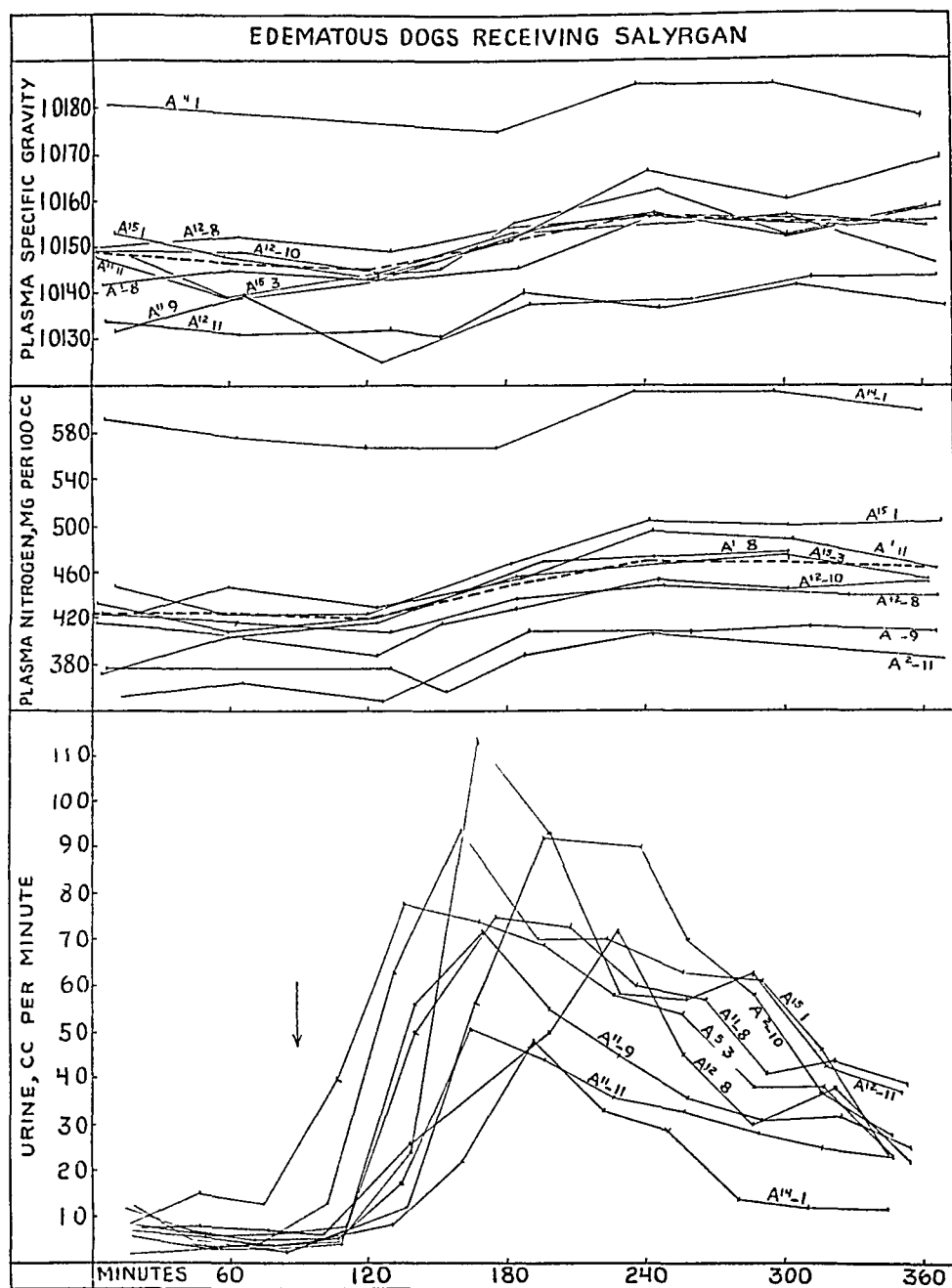


Fig 4—Chart showing the effect of the administration of salyrgan on the specific gravity and the total nitrogen content of the plasma and the volume of urine in edematous dogs

water and salyrgan were given (fig 2) the diuresis was somewhat more marked than with water alone, but an interpretation of the curve of the specific gravity of the plasma is rendered difficult by the drop in the

curve found in the control experiments with water alone. These considerations also apply to the colloid osmotic pressure. We consider that these experiments in normal dogs show no significant changes in the specific gravity or in the colloid osmotic pressure of the plasma which can be attributed to salyrgan alone. For this reason further studies on normal dogs were not carried out.

In edematous dogs (figs 3 and 4 and the table) the results were more striking. The control experiments (fig 3) showed minor variations in the specific gravity and the total nitrogen content of the plasma without showing any constant tendency for these values to become elevated or lowered during the course of six hours. The urinary output also tended to remain fairly constant, and there was no evidence of spontaneous diuresis during the experiment except in one instance in which the output of urine remained constantly above 1 cc per minute. The administration of salyrgan (fig 4) produced a definite, prolonged diuresis in these animals, the increased urinary flow began from one-half to one hour after the drug was given, reached a maximum of from 5 to 11 cc per minute in one or two hours and declined gradually during the remainder of the experiment. In the period between the administration of salyrgan and the onset of diuresis, only minor fluctuations occurred in the specific gravity and in the nitrogen concentration of the plasma which were no greater than those found in the control experiments. In only one of five instances did the colloid osmotic pressure show during this fore period a fall that was greater than the limits of error of the method (table). In the remaining four instances there was no appreciable change in the pressure as measured before and one-half hour after the administration of salyrgan. Coincident with the onset of the diuresis there was noted in every experiment a moderate but definite and continued rise in the specific gravity and in the total nitrogen content of the plasma. This rise was more constant in occurrence and longer in duration than could be attributed to sporadic variations. Similarly, in the experiments in which the colloid osmotic pressure was measured during the period of diuresis there was found a significant rise above the prediuresis level, as has been observed commonly by other investigators.

#### COMMENT

In recent years a number of studies have been made of the changes which occur in the concentration of such blood and plasma constituents as the erythrocytes, the hemoglobin, the protein and the chlorides following the administration of mercurial diuretics. These investigations have sought to establish the presence of a dilution of the blood which indicates an extrarenal action of the drug or of a concentration indicating that the action is directly on the kidney. The possibility that these

actions occur at different times also has been considered. If, for example, it was observed that following the injection of the diuretic a dilution and later a concentration of the blood occurred, the interpretation was that the diuretic had exerted at first an action on the extrarenal tissues and later a direct action on the kidney.<sup>4</sup> The validity of this method of attack rests on two assumptions: first, that fluid from the tissues can accumulate in the blood in detectable amounts before being removed by the kidney or, on the other hand, that the kidney can remove fluid from the blood with sufficient rapidity to cause a detectable concentration; second, that the total quantity of the constituent the concentration of which is measured remains constant in the blood stream during the period of observation. It follows from the latter assumption that changes in the concentration of the constituent are to be interpreted as representing an addition to or a loss of fluid from the blood stream, i. e., changes in the volume of the blood. Plasma proteins appear to be the ideal constituent for this study because their concentration can be measured accurately by a number of methods and because they are generally regarded as being relatively nondiffusible. Most investigators, with the exception of Nonnenbruch,<sup>17</sup> have felt that following the administration of mercurial diuretics no protein is added to the blood stream and the volume of blood is the variable factor.

In our investigation we have sought evidence of dilution or of concentration of blood after the administration of salyrgan by studying the changes in the plasma protein content as reflected in the specific gravity, the total nitrogen content and the colloid osmotic pressure of the plasma. The significant observations were those made on edematous dogs, in which the diuresis resulting from the administration of salyrgan is large and the experiment is not complicated by the administration of water. In these animals the absence of any appreciable changes in the factors measured before the onset of the diuresis speaks against the occurrence of a dilution of the blood (i. e., of an extrarenal action) during this period. On the other hand, the finding of an increase in the specific gravity, the total nitrogen content and the colloid osmotic pressure coincident with the diuresis indicates that during this later period a concentration of the blood occurred. If it is assumed that no protein had been added to the blood stream, then the concentration must have been due to a loss of fluid with a resulting decrease in the volume of blood. This suggests that during the diuresis the kidney removed fluid from the blood more rapidly than fluid was supplied from the tissues. It appears from this that the kidney was responding to a direct stimulus. These observations, though not necessarily excluding the possibility of some extrarenal action of salyrgan, indicate that the effect of the drug is predominantly on the kidney.

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17 Nonnenbruch, W. Ueber Diurese, *Ergebn d inn Med u Kinderh* **26** 119, 1924

## SUMMARY

Studies are reported concerning the effect of the diuresis following the administration of salyrgan on the specific gravity and the colloid osmotic pressure of the plasma in normal dogs and on these same factors plus the total nitrogen content of the plasma in dogs made edematous by plasmapheresis and by the feeding of salt and a low protein diet

When salyrgan was administered alone to normal dogs, the diuretic response was slight and was not accompanied by any significant changes in the plasma specific gravity or in the colloid osmotic pressure

Following the administration of water by mouth, a fall occurred in the measurements which was not significantly altered when water and salyrgan were administered together

In edematous dogs salyrgan produced a marked and prolonged diuresis. No significant changes were observed in the specific gravity, the total nitrogen content or the colloid osmotic pressure of the plasma before the onset of diuresis. Coincident with the diuresis, however, a sustained rise in all of these values occurred

The findings are discussed in relation to current theories of the action of salyrgan as affording no evidence of an extrarenal action and indicating predominantly a direct effect on the kidney

# PITUITARY BASOPHILISM

## REPORT OF A CASE

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AND

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NEW HAVEN, CONN

Cushing<sup>1</sup> recently described a syndrome characterized by obesity of unusual distribution, hirsuties, pigmentation of the skin, purpura, abdominal striae, hypertension, glycosuria and skeletal decalcification developing in relatively young persons, usually in women, whose complaints are chiefly amenorrhea, obesity, body pains and weakness. Many of this group of patients had previously been included in the group with adrenal tumor. Including his own cases and those in the literature, Cushing collected fifteen instances of this syndrome, in most of which a basophilic adenoma of the pituitary gland was noted at necropsy. He also reported other cases of the syndrome in patients who are still living. We wish to report in this paper a striking example of this syndrome, in which the condition was recognized during life and the diagnosis confirmed by postmortem examination.

## REPORT OF CASE

*History*—F Q, a man aged 44, single, an editor and writer, entered the New Haven Hospital by ambulance at 9 30 p m on Feb 3, 1934. He was referred with the diagnosis of coronary occlusion, owing to the fact that he was suffering from severe pain in the chest.

Four days before his admission he had gone for a walk in the cold air and on returning had had discomfort in the chest. After eating a hearty meal he was seized with a severe, smothering thoracic pain, not sharply localized but radiating to the back. A physician prescribed morphine, but repeated doses were necessary to give relief. Pain radiating down the left arm developed, and two days later attacks of dyspnea, characterized by wheezy breathing and orthopnea, appeared. Owing to continued pain, dyspnea and restlessness, his physician advised his coming to the hospital.

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1 Cushing, Harvey (a) *The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism)*, Bull Johns Hopkins Hosp 50 137, 1932, (b) *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Ill, Charles C Thomas, Publisher, 1932, p 234, (c) *Further Notes on Pituitary Basophilism*, J A M A, 99 281 (July 23) 1932, (d) "Dyspituitarism" Twenty Years Later, Arch Int Med 51 487 (April) 1933.

*Family History*—One brother of the patient had had a "nervous breakdown" the preceding autumn and at the time was taking thyroid extract because of a low basal metabolic rate. There was no important familial disease.

*Past History*—Until four years prior to his admission the patient had been well and had taken good care of himself. In 1924, 1925 and 1926 he had health examinations at a life extension institute. The following data are extracted in part from these records:

Date	1924	1926	1934	(New Haven Hospital)
Height, feet, inches	5-9½	5-10	5-7	(post mortem)
Chest, inches	37	40	39	(post mortem)
Abdomen, inches	35½	39	36½	(post mortem)
Weight, pounds	173	184½	152	(post mortem)
Percentage of hemoglobin	93	81	80	
Pulse rate	76	82	100	
Temperature	No record	No record	101 F	
Blood pressure	134/90	118/82	From 150/90 to 175/120	
Sugar in urine	None	None	Glycosuria	

In 1926 a slight scoliosis was noted, the right shoulder was higher than the left, the pupils were unequal, there was tremor of the fingers, the abdomen was pendulous, dry râles were heard at the end of inspiration.

As a young man the patient had been rather slender and well proportioned (fig 1A). Until 1929 he had considered himself well. From that time he had complained of the following symptoms: increasing weakness during the past five years, loss of libido of five years' duration, lumbago for four years, characterized by frequent attacks of severe pain in the dorsal portion of the spine, necessitating rest in bed, asthma, often associated with, but sometimes independent of, the attacks of lumbago, characterized by severe dyspnea and orthopnea and unrelated to exertion, infection or the common allergic factors, nocturia and frequency during the past year, hemorrhage from the throat one year before admission, edema of the ankles, slight falling of the hair and drooling of saliva at night for three months. Four years prior to admission pain and swelling developed in the left knee, and since then he had had considerable difficulty in walking. He also had had severe pain in both knees and ankles, which at times lasted a day or two. During the last three years he had had a chronic eruption on the skin of the nose. During the past year ecchymotic spots had appeared on the skin over the entire body on the slightest injury, and sometimes spontaneously. For the past ten years he had been known to have a red face.

*Physical Examination*—On admission the patient's temperature was 101.5 F, the pulse rate 100 and the respiratory rate 38. The blood pressure measured 150 systolic and 110 diastolic.

The patient was a florid man, who was breathing rapidly and with slight wheezing, he was propped up in bed and complained of severe pain in the anterior part of the chest on both sides. He had difficulty in localizing the pain. He was intelligent and cooperative. The head, neck, chest and abdomen seemed disproportionately large when compared with the relatively thin arms and legs. The cheeks were thick and fat, and there was adiposity of the neck, the supraclavicular regions and the abdomen, which was protuberant. The neck was short, and the shoulders were rounded. Dorsal kyphosis was evident, and the patient gave the impression of having lost height (figs 1B and C).

Several purpuric spots were present over the skin of the arms and legs, and there was marked pigmentation of the skin on the anterior surface of the lower portions of the legs. On the lower portion of the abdomen on the right side there was one

stria atrophica about 2 inches (5 cm) long and  $\frac{1}{2}$  inch (127 cm) wide. The hair was abundant and graying. The vessels of the face and cheeks were dilated. The eyes were somewhat prominent, and there were soft pads of fat beneath both upper lids in the upper and outer portions. The left pupil was slightly larger than the right, and both pupils reacted normally to light and in accommodation. The fundi were normal except for slight blurring of the disks. The visual fields were normal, as tested roughly.

The tongue was heavily coated, the teeth were in poor condition, and many were carious. The thyroid gland was not enlarged. The chest was of the

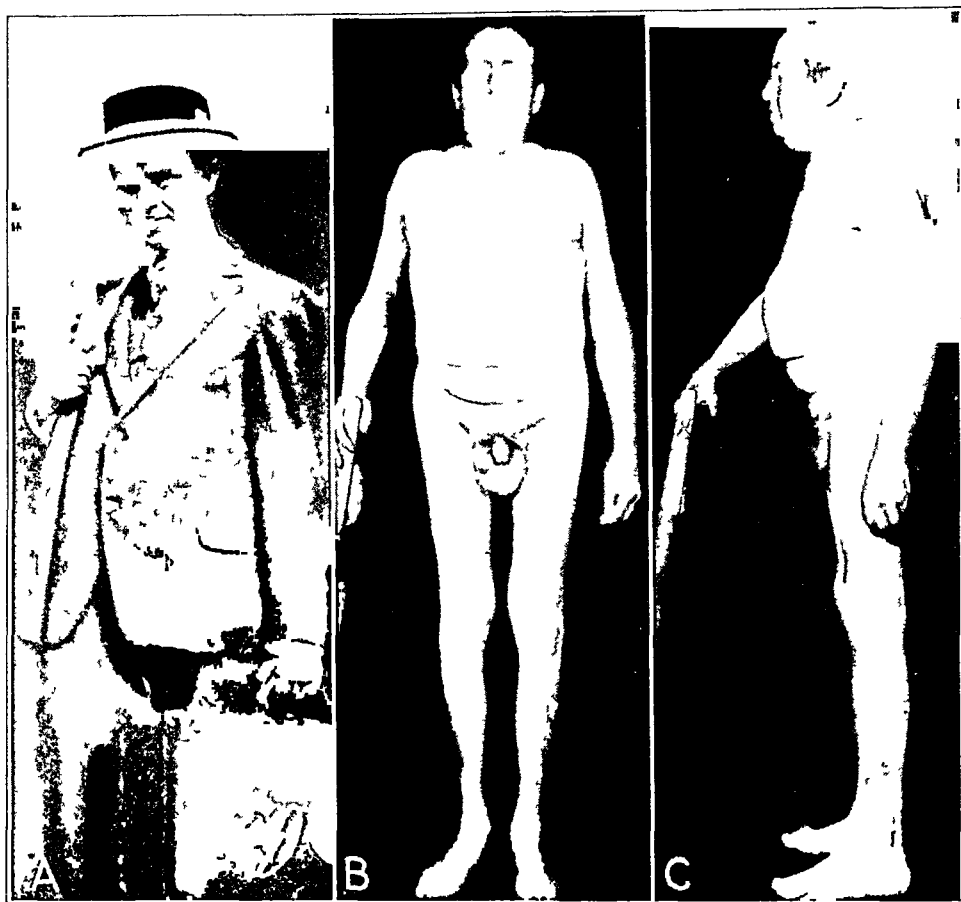


Fig 1—Photograph of the patient. *A* was taken at the age of 24, *B* and *C*, on admission to the hospital. *B* shows the spindling extremities and protuberant abdomen, and *C*, dorsal kyphosis and facial adiposity.

emphysematous type, and the anteroposterior diameter was markedly increased. The lungs were hyperresonant throughout, and there were numerous rhonchi and coarse rales with asthmatic breathing throughout both lungs. The heart did not seem enlarged (the autopsy protocol may be compared). The sounds were distant but of good quality, and there were no murmurs. The pulse was regular and of good quality, the radial vessels were not remarkable. The abdomen was adipose, protuberant and moderately distended, but no organs or masses were felt. The genitalia were normal in development. Neurologic examination revealed nothing abnormal. Taste and olfactory sensation were not tested.



*Laboratory Data*—The blood count was as follows white cells, 15,800, polymorphonuclears, 69 per cent, lymphocytes, 23 per cent, large mononuclears, 8 per cent, red cells, 4,060,000, hemoglobin, 80 per cent. The cells in the smear appeared to be of normal type.

Examination of the urine revealed a clear, yellow color, a specific gravity of 1.029, a slight trace of albumin, and a negative reaction for sugar. The sediment contained occasional white blood cells but no red cells or casts. Subsequent daily examinations of the urine showed a slight trace of sugar on several occasions.

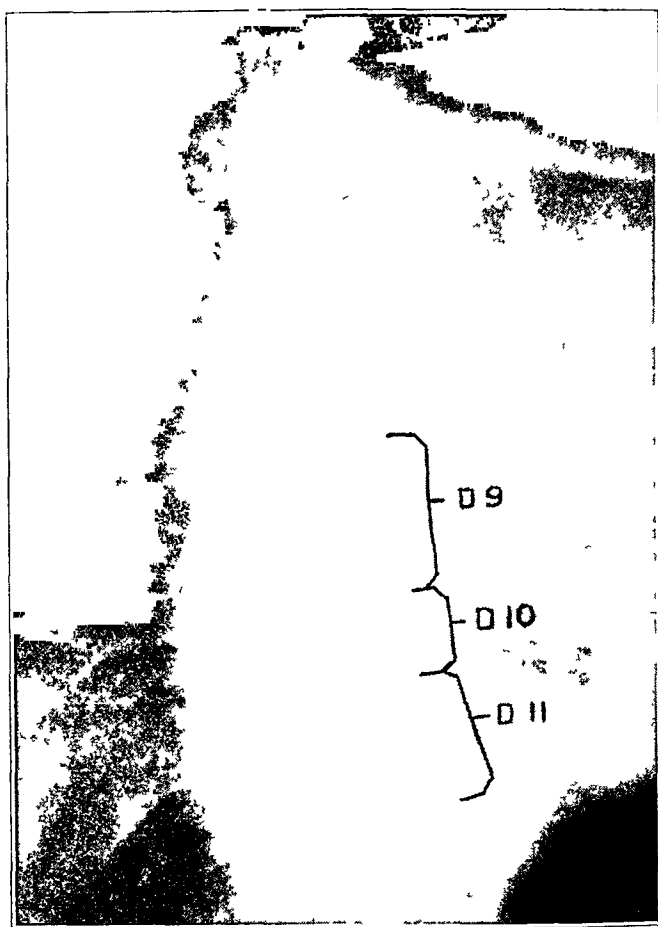


Fig 2—Roentgenogram showing the demineralization of the spinal column and compression of the tenth dorsal vertebra.

The Kahn reaction was negative. The blood, as shown by the results of typing (Jansky), belonged to group 1. The bleeding time was three minutes, the clotting time, two minutes, and the number of platelets, 320,000.

The electrocardiogram showed a normal mechanism.

The striking clinical picture of obesity of unusual distribution, abdominal striae, purpura, pigmentation of the skin, kyphosis and apparent shortening of the spine, hypertension and glycosuria suggested Cushing's syndrome or pituitary basophilism. The diagnosis of primary hyperparathyroidism was also considered.

Further laboratory studies were made. The blood chemistry was as follows: Nonprotein nitrogen, 56 mg per hundred cubic centimeters (four days after admis-

sion), total serum proteins, 5.41 mg, albumin, 3.49 mg, globulin, 1.92 mg, ratio of albumin to globulin, 1.2, serum calcium, 8.94 mg, serum phosphorus, 8.15 mg; total fatty acids of serum, 9 milliequivalents (eleven days after admission), serum lipoid phosphorus, 7 mg, and serum cholesterol, 123 mg

The results of the sugar tolerance test were as follows: blood sugar after fasting, 88 mg per hundred cubic centimeters, five minutes after the intravenous injection of 35 Gm of dextrose, 236 mg, fifteen minutes after injection, 217 mg, thirty minutes after injection, 203 mg, forty-five minutes after injection, 189 mg, sixty minutes after injection, 178 mg, and one hundred and twenty minutes

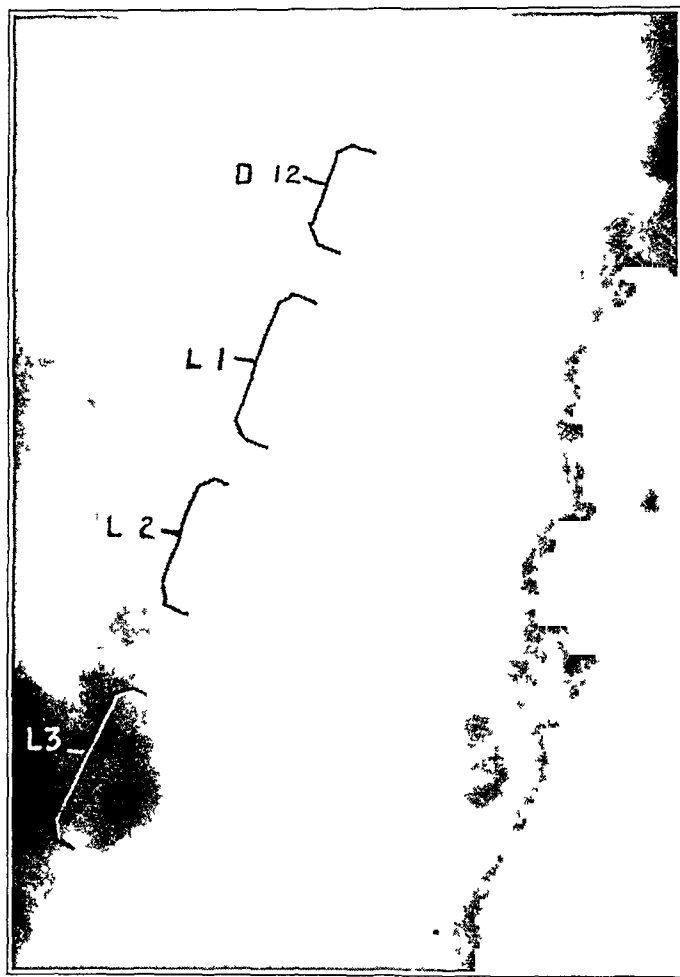


Fig 3—Roentgenogram showing compression of the twelfth dorsal and second lumbar vertebrae

after injection, 120 mg. It is evident that the patient had a decreased sugar tolerance.

Roentgenograms of the complete skeleton revealed marked and striking generalized decalcification. There was no evidence anywhere of destruction of the trabecular structure or of isolated areas of more marked decalcification, suggestive of osteitis fibrosa cystica. Two old fractures were present in the twelfth rib on the right side, and there were compression fractures of the tenth and twelfth thoracic and second lumbar vertebrae (figs 2 and 3). The fifth lumbar vertebra was slightly more narrowed than normally, and the intervertebral spaces above

and below it were widened. The seventh dorsal vertebra was also narrowed in its craniocaudal dimension. The femoral arteries showed marked calcification (fig 4).

In view of the extensive demineralization of the skeleton, studies of the calcium balance were made by Dr C L Robbins. The report follows: "The calcium and phosphorus balances were within the limits of normal variation. The metabolism of these elements certainly did not conform to the pattern described as typical of hyperparathyroidism. In repeated studies of the blood it was found that the serum calcium was normal in amount and that the concentration of inorganic phosphorus varied, apparently without relation to the level of serum calcium."

*Calcium and Phosphorus Metabolism Calculated for a Three Day Period*

Subject	Calcium					Phosphorus				
	Urine, Gm	Stools, Gm	Total Excre- tion, Gm	Intake, Gm	Bal- ance, Gm	Urine, Gm	Stools, Gm	Total Excre- tion, Gm	Intake, Gm	Bal- ance, Gm
F Q	0.21	1.19	1.40	1.07	-0.33	1.59	0.67	2.26	0.84	-1.42
Normal subject*	0.25	1.53	1.78	1.50	-0.28	2.56	0.91	3.47	2.94	-0.53
Patient with hyperparathyroidism†	0.96	3.12	4.08	1.68	-2.40	3.93	0.23	4.16	2.70	-1.46

\* The figures represent the calculated averages of the values obtained for six normal persons used as controls (C L Robbins).

† Data were taken from studies on the first patient described by Bulger and his co-workers (Bulger, H A, Dixon, H H, Burr, D P, and Schregardus, O. The Functional Pathology of Hyperparathyroidism, J Clin Investigation 9 143, 1930).

"In the table the patient's excretion of calcium and phosphorus is compared with that of normal persons and of a patient with hyperparathyroidism studied under similar experimental conditions. The total excretion of calcium and its partition between the urinary calcium and that of the stools were well within normal limits. It is obvious that a normal economy of calcium could not always have prevailed. The conclusion may be drawn merely that at the time at which the patient was studied no clues as to the mechanism of the decalcification of bone were detectable. The excretion of phosphorus greatly exceeded the intake, but this is usually the case when there is rapid destruction of body protein due to fever and insufficient intake of food."

Cushing<sup>2</sup> reported the presence of a follicle-stimulating hormone in the urine of one of his patients. With this in mind, Dr S B D Aberle studied the urine and blood serum of our patient for the presence of this hormone.<sup>3</sup> In immature mice and rats from 19 to 23 days of age, varying amounts of the patient's urine and blood serum were injected subcutaneously, and the animals were killed after one hundred hours. The ovaries were then fixed, sectioned and studied for evidence of follicular maturation and luteinization. It was noted that approximately 5 cc of blood serum produced follicular maturation (follicular maturation is known as reaction 1 of Zondek and Aschheim<sup>4</sup>) and that 6 cc of urine gave a similar effect, suggesting that the serum and urine contained equal amounts of

2 Cushing,<sup>1d</sup> p 524

3 These observations were aided by funds from a grant from the National Research Council, Committee on Problems of Sex, administered by Dr S B D Aberle.

4 Zondek, B, and Aschheim, S. Das Hormon des Hypophysenvorderlappens I. Testobjekt zum Nachweis des Hormons, Klin Wchnschr 6 248, 1927.

the hormone Luteinization did not take place even when the urine had a concentration twenty times that of the normal. Two specimens of normal urine used as controls gave negative reactions both for follicular maturation and for luteinization.

*Course and Treatment*—From the time of his admission until his discharge the patient continued to have more or less severe parasternal and subscapular pain, with acute exacerbations necessitating the giving of morphine. Often there was associated numbness of the left hand and of the toes of the left foot. At times

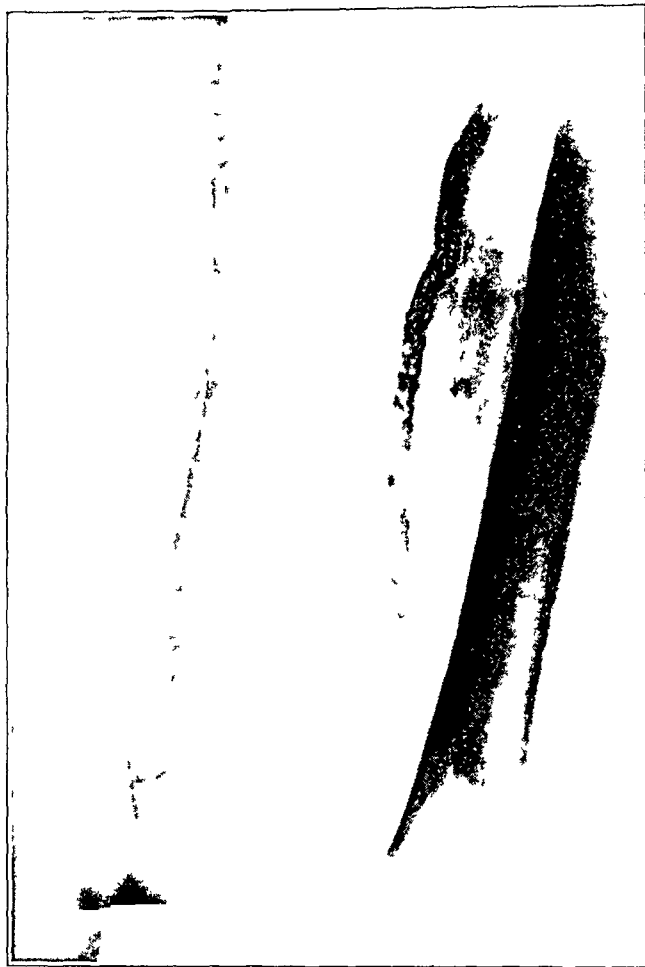


Fig. 4—Roentgenogram revealing calcification in the femoral vessels

he suffered from girdle pains over the middle and lower thoracic regions. Since vertebral collapse was present, he was placed on a Whitman frame.

On his admission to the hospital it was noted that his teeth were in poor condition. For two years he had had intermittent toothache in the right maxillary region. On the second day of hospitalization he had considerable pain in the upper and lower jaws on the right side. Examination revealed gingivitis and formation of pockets around some of the teeth, and roentgenograms revealed abscesses about several of them. Marked swelling and tenderness developed in the submaxillary and submental regions of the right side. Two of the abscessed teeth from the upper and lower jaws on the right side were removed by Dr. B. G. Anderson on February 8. Heat was applied to the neck and jaw and supportive

treatment was given, but the patient did not improve. He continued to have a moderately high temperature and leukocytosis. On February 12 there was increasing bilateral swelling and induration of the submental region. The floor of the mouth was raised and indurated. On February 12, under procaine hydrochloride anesthesia, Dr. E. B. Hopper incised and drained bilateral sublingual abscesses and obtained 20 cc of pus from which hemolytic streptococci and staphylococci were cultured.

After drainage of the abscesses the patient did not improve. He was unable to take fluids by mouth, and frequent infusions and transfusions were necessary. A temperature of from 101 to 102 F continued, and signs of bronchopneumonia



Fig. 5—Section of the adrenal gland showing cortical hyperplasia and an adenoma. Hematoxylin and eosin stain,  $\times 11$ .

developed. Edema of the lower extremities was noted. Suddenly at 10:45 p. m. on February 16, he gasped for breath, the pulse became thready, the blood pressure was not obtainable, and after stimulants failed to revive him he died, apparently as a result of circulatory failure.

*Necropsy*—The examination was performed four hours post mortem by Dr. Dan S. Egbert. An abstract of the protocol follows.

The body weighed 69 Kg (152 pounds) and measured 168 cm (5 feet and 7 inches) in length. Numerous subcutaneous ecchymoses were present over the hands and arms. A network of fine subcutaneous vessels imparted a ruddy hue to the cheeks. Over the anterior surfaces of both legs the skin was shining, thin and bronzed, elsewhere it was pale, dry and scaling. There was pitting edema

over the wrists and the dorsa of the hands and ankles. The distribution of hair over the body was that of the normal adult man. There was no enlargement of the superficial lymph nodes.

The tissues over and beneath the mandible were swollen and indurated. Two transverse incisions, each 3 cm. in length, on either side of the midline in the submental region were connected by a through-and-through rubber drain. The edges of these incisions were soft and covered with purulent material which oozed from the wounds. The thyroid gland was not enlarged to palpation. The chest was large and barrel-shaped, the abdomen was round and protuberant. Subcutaneous fat over the chest measured 2.8 cm. in thickness, and over the abdomen, 1.8 cm.

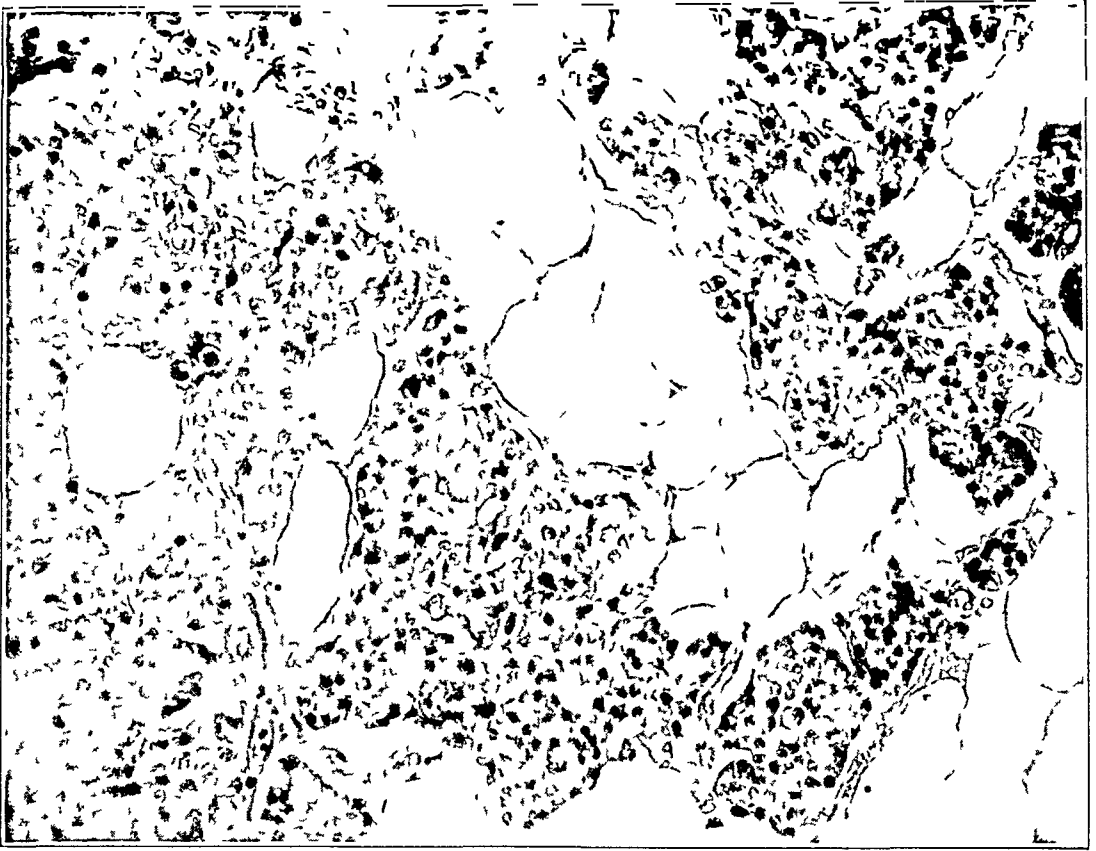


Fig. 6—Section from the parathyroid gland showing the infiltration of adipose tissue. Hematoxylin and eosin stain,  $\times 200$ .

A small amount of adipose tissue in the anterior portion of the mediastinum was all that remained of the thymus. Freshly clotted blood completely filled the left pleural cavity and compressed the lung against the mediastinum, displacing the heart to the right. About 50 cc. of sanguineous fluid was present in the right pleural cavity, and a similar quantity was noted in the pericardial sac. The superior and inferior venae cavae were greatly distended with blood. The source of the extensive pleural hemorrhage was observed to be a dissecting aortic aneurysm which had burrowed its way through the mediastinal tissues into the left pleural cavity. This aneurysm commenced at the site of two large intimal tears in the isthmus of the aorta and had worked its way between the inner and outer coats of the media to the bifurcation of the common iliac arteries, extending for a short distance in the wall of the right iliac vessel. Numerous large and small atherom-

atous plaques, some of which were ulcerated, studded the intima of the whole aorta. Similar lesions encroached on the lumens of both coronary arteries and their major divisions, producing almost complete occlusion of the descending branch of the left coronary artery. The heart was hypertrophied to a marked degree and weighed 500 Gm.

The only change of note in the lungs, liver, spleen and pancreas consisted of uniform thickening of the walls and consequent narrowing of the lumens of the arteries and arterioles of these organs. Both adrenals were much larger than the normal gland, the right adrenal weighed 18 Gm and the left 15 Gm. The cortices were bright orange-yellow and were two or three times wider than the normal cortex, whereas their medullas were narrow and had the usual red-brown color. The left adrenal contained several sharply circumscribed cortical adenomas, which varied from 2 to 5 mm in diameter (fig. 5).

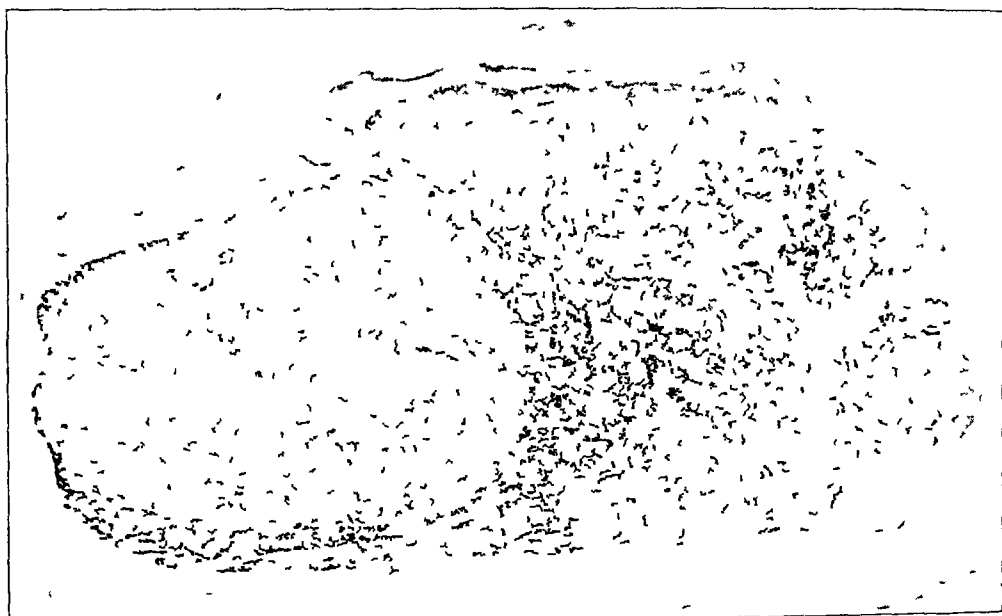


Fig. 7—Adenoma of the parathyroid gland occupying the left half of the gland. Hematoxylin and eosin stain,  $\times 20$ .

The right kidney weighed 152 Gm and the left 160 Gm. Each kidney was of normal size and presented no scars on external examination. A few glomerular lesions were encountered on microscopic examination, and these consisted of the usual complete fibrosis and hyalinization. There were no arteriolar changes, and few of the larger arteries showed advanced atheromatous lesions. The uriniferous tubules were intact.

The prostate gland presented no abnormalities either on gross or on microscopic examination. Active spermatogenesis was observed in both testes, although the seminiferous tubules were widely separated as though by edema, the interstitial cells were in a good state of preservation. Nothing of pathologic import was found in the thyroid gland. Only two small ovoid bodies, each measuring 3 mm in the greatest diameter, were positively identified as parathyroid glands. The first body presented an atrophic appearance on microscopic examination, the normal structure being replaced to a large extent by adipose tissue (fig. 6). About one

third of the second parathyroid gland was represented by an adenoma (fig 7) Both bodies were sectioned serially, and each section was mounted and stained A careful search through the entire thyroid gland failed to expose more parathyroid tissue

The skeleton showed marked changes The bones were unusually soft, especially the ribs and calvarium The outer compact layer of the long bones was of the usual thickness and contained no nodules or cysts Its softness appeared to be due to a diminished amount of inorganic material The periosteum appeared normal, and osteoclasts were not seen The marked kyphosis and scoliosis of the thoracic portion of the spinal column were the result of old fractures of the bodies



Fig 8—Section of the pituitary gland showing the normal pars anterior on the left, colloid in cysts of the pars intermedia and infiltration of basophils in the pars nervosa on the right Hematoxylin and eosin stain,  $\times 50$

of the tenth and twelfth thoracic vertebrae and of the second lumbar vertebra, which were due to compression and had since healed

The cerebral meninges and parenchyma were edematous An old vascular lesion replaced the dorsal half of the left claustrum and the adjacent dorsal portion of the putamen, but no other lesions were observed in the cerebral parenchyma The lateral ventricles were not dilated, but the third ventricle was distinctly enlarged The posterior recess of this cavity projected as a diverticulum into the pineal body, which consequently was enlarged and measured 13 by 10 by 8 mm On microscopic examination this body presented a normal picture The infundibular portion of the third ventricle was not completely lined by ependyma, for several breaks in the lining occurred at frequent intervals In the adjacent



tissue could be seen numbers of clear spaces of various sizes These spaces represented accumulations of tissue fluid (edema) or other substance which had become dissolved out in the process of embedding

**Pituitary Body** The hypophysis was not increased in size and measured 18 by 10 by 5 mm It was removed in its dural envelop, fixed in a diluted solution of formaldehyde U S P (1 10) and embedded whole in paraffin Serial sections were cut in a horizontal plane, as recommended by Cushing,<sup>5</sup> and stained with hematoxylin and eosin

The neurohypophysis was sparsely invaded by a number of basophilic cells which lay chiefly in two clusters (fig 8) The cytoplasm of these cells stained

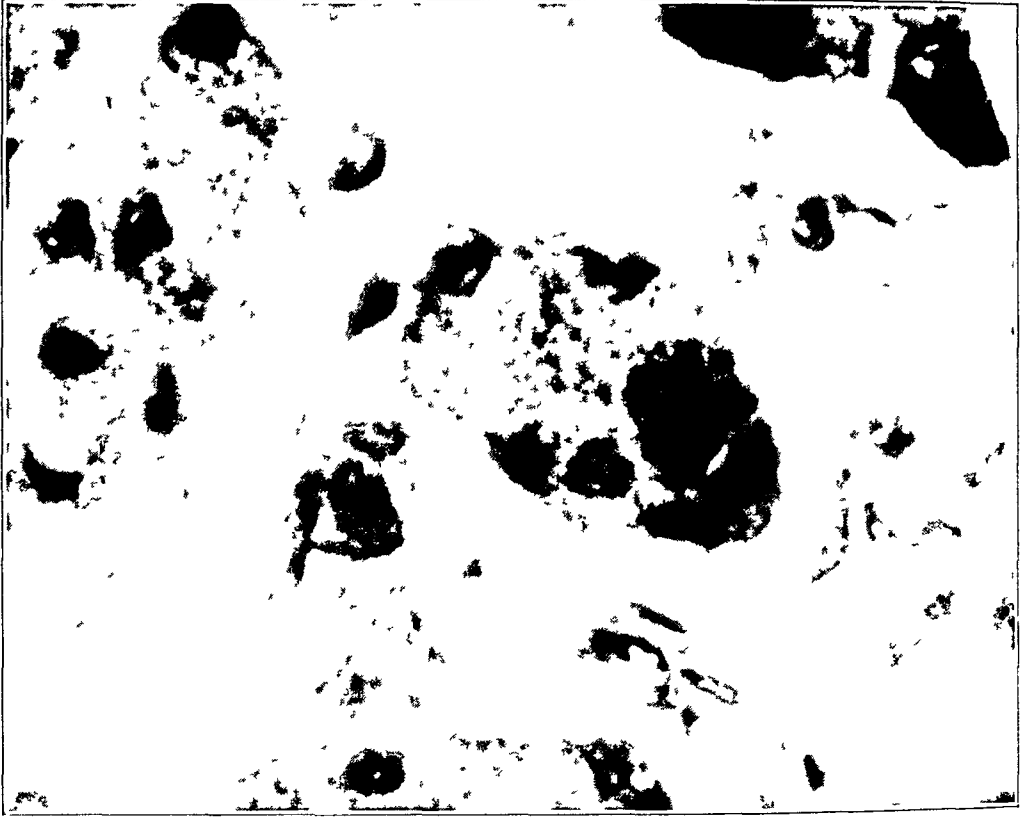


Fig 9—Basophilic cells in the pars nervosa showing large granules in the cytoplasm Hematoxylin and eosin stain,  $\times 750$

deeply and contained numerous large granules (fig 9) Frequently the cells had more than one nucleus Several small cystlike cavities, which were partially lined by flattened epithelium, were also present in the pars posterior These spaces contained pink-staining colloid in which could be seen occasionally the remnants of nuclei In the pars intermedia a huge cavity containing colloid almost completely separated the anterior from the posterior lobe of the hypophysis This cavity also was lined by flattened epithelium

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5 Cushing, Harvey Posterior Pituitary Activity from an Anatomical Standpoint, *Am J Path* 9 539 (Sept) 1933

In the upper anterolateral angle of the pars anterior was observed an oval, papillary, basophilic adenoma which measured 4 mm in its greatest diameter (fig 10). This was situated immediately beneath the dural envelop of the pituitary gland, and its discovery was due to the precaution in removing the gland encased in its dura, for had the latter membrane been stripped before embedding, at least part of the adenoma would have been destroyed. The tumor, indeed, lay in part within the layers of the dura. A thin capsule of connective tissue separated the normal pars anterior from the adenoma. At one end of the adenoma a large pool of dark-staining, inspissated, colloid material was situated. On the whole the cells comprising the adenoma were not as large as the basophilic cells seen in the pars posterior. The cytoplasm was stained less deeply. In many

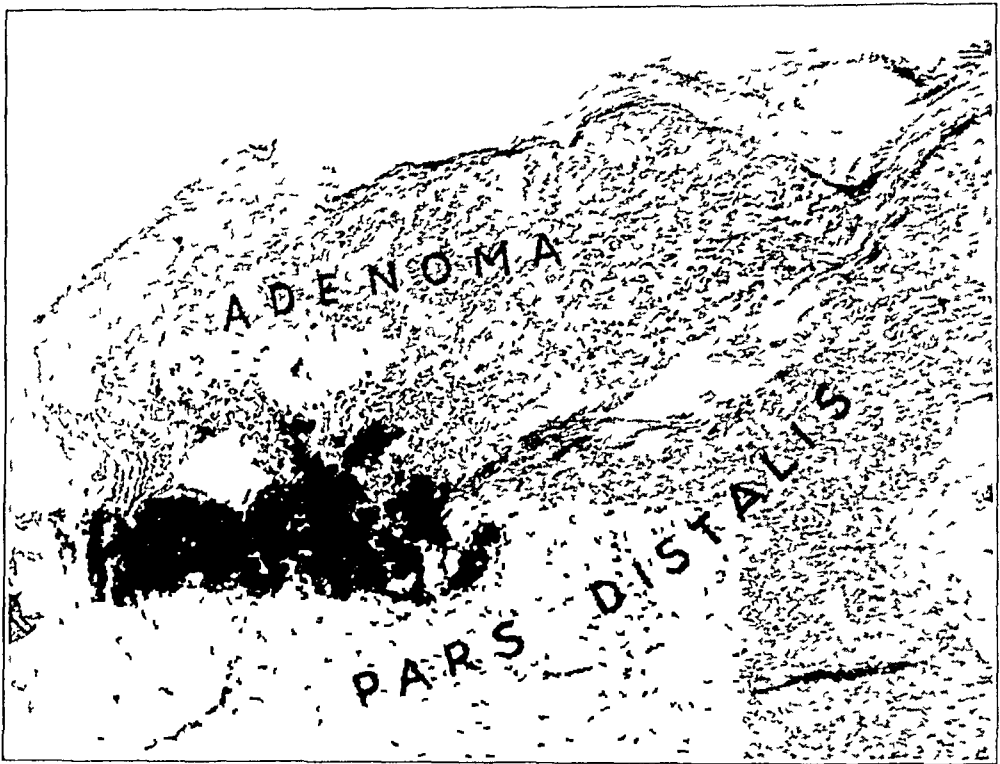


Fig 10—Basophilic adenoma beneath the dura covering the pars anterior of the pituitary body with colloid at lower border of the tumor on the left side. Hematoxylin and eosin stain,  $\times 30$ .

of the cells no granules were demonstrable, but this condition was variable, for some presented a typical basophilic appearance, even as regards the presence of more than one nucleus in a cell and the characteristic vacuolation of the cytoplasm.

#### COMMENT

Since Cushing's Harvey Society Lecture,<sup>1d</sup> in which he cited thirteen cases from the literature assumed to be instances of pituitary basophilism and added two cases of his own, further examples of the syndrome with verification at necropsy have been reported by Rutishauser

(case 1),<sup>6</sup> Marburg<sup>7</sup> and Craig and Cran<sup>8</sup> These cases with our own bring the total to nineteen verified cases Dr Cushing, in a personal communication, stated that he has received descriptions of six other verified cases as yet unpublished

This case presented several unusual features The basophilic adenoma in the anterior lobe of the pituitary gland, although of macroscopic size (4 mm in the greatest diameter), did not appear active on microscopic examination Many of the cells, as already mentioned, were rather small and contained few granules The presence of inspissated colloid in the tumor may also be interpreted as evidence of low functional activity Dr Cushing, who examined these preparations, was of the opinion that the activity of the adenoma was burned out, that the tumor quite likely had been active in the past but was at present in a dormant state More evidence of basophilism was observed in the large accumulation of colloid in the pars intermedia and in the infiltration of basophilic cells in the neurohypophysis

The clinical signs of basophilism, such as facial, thoracic and abdominal adiposity, bronzed skin, stria atrophica, glycosuria, ecchymoses and striking skeletal decalcification, were fairly characteristic of Cushing's syndrome The blood pressure, which is always elevated in this condition, varied between 150 and 175 systolic in our patient, but on admission he already had symptoms suggestive of the dissecting aortic aneurysm of which he died It is therefore conceivable that his blood pressure at some time previous to his admission to the hospital was even more elevated This appeared all the more likely from the presence of marked arteriolar sclerosis in the viscera, exclusive of the kidneys

Anatomically, in addition to the pituitary adenoma, cortical hyperplasia and adenomas were noted in the adïrenal glands A similar solitary cortical adenoma in the adïrenal has previously been noted only in the case described by Anderson<sup>9</sup> (case 3 of Cushing's series) Another feature of unusual interest in our case was the presence of the small adenoma in one of the parathyroid glands This condition has pre-

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6 Rutishauser, E Osteoporotische Fettsucht (Pituitary Basophilism), *Deutsches Arch f klin Med* **175** 640, 1933

7 Marburg, O Ueber das basophile Adenom der Hypophyse, die zerebrale Fettsucht und die Pseudohypertrophie der Muskeln, *Arb a d neurol Inst a d Wien Univ* **35** 143, 1933

8 Craig, J, and Cran, B Basophil Adenoma of the Pituitary Gland, *Quart J Med* **3** 57 (Jan) 1934

9 Anderson, J A Case of Polyglandular Syndrome with Adrenal Hypernephroma and Adenoma in the Pituitary Gland—Both of Small Size, *Glasgow M J* **83** 178, 1915

viously been noted only in the case of Schmorl<sup>10</sup> and Molineus<sup>11</sup>. It is possible that the adenomas of the adrenal and parathyroid glands were secondary to the pituitary adenoma. The usual associated anatomic evidence of extreme hyperparathyroidism, namely, von Recklinghausen's disease, was absent, there were no cysts and fibrosis in the bones, although the latter structures were markedly decalcified. Moreover, studies on the calcium metabolism in our patient did not show the usual picture of hyperparathyroidism. However, it seems reasonable to relate the adenoma of the parathyroid to the skeletal decalcification.

#### SUMMARY

The case is described of a white man, aged 44, who presented the clinical features of Cushing's syndrome of pituitary basophilism. The patient died as the result of a ruptured dissecting aortic aneurysm and cervical cellulitis. Postmortem examination revealed an inactive basophilic adenoma of the anterior pituitary gland, cortical hyperplasia and adenomas of the adrenal glands, an adenoma of one of the parathyroid bodies and diffuse skeletal demineralization.

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10 Schmorl, C. G. Ein Fall von deformierender Osteitis, *München med Wchnschr* **59** 2891, 1912.

11 Molineus. Ueber die multiplen braunen Tumoren bei Osteomalacie, *Arch f klin Chir* **101** 333, 1913.

# CARDIAC PAIN

## PRESENCE OF PAIN FIBERS IN THE NERVE PLEXUS SURROUNDING THE CORONARY VESSELS

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AND

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The most generally accepted explanation for the occurrence of pain in angina pectoris is the theory of cardiac ischemia. This theory is supported by several lines of evidence (the recent literature is reviewed by Keefer and Resnik<sup>1</sup> and Lewis<sup>2</sup>), one of which is based on animal experiments. This last type of evidence consists of the demonstration by Sutton and King,<sup>3</sup> Pearcy, Priest and Van Allen<sup>4</sup> and Sutton and Lueth<sup>5</sup> of pain responses following occlusion of the coronary arteries in unanesthetized animals. These observers reported that pain was produced immediately on occlusion of the coronary arteries and that this pain ceased as soon as the vascular occlusion was released. Sutton<sup>6</sup> stated "In these experiments careful observations have been made on the effect of the temporary occlusion of the coronary arteries in unanesthetized animals, with the conclusion that temporary occlusion results in immediate pain. It has been shown that this pain is the result of decreased nutrition to the heart muscle and not the result of trauma to nerve fibres." Singer,<sup>7</sup> in studies antedating the others, claimed that

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Aided by the Frederick K. Babson Fund for the Study of Diseases of the Heart and Circulation, Michael Reese Hospital

From the Cardiovascular Laboratory, Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago

1 Keefer, C. S., and Resnik, W. H. Angina Pectoris, *Arch Int Med* **41** 769 (June) 1928

2 Lewis, T. Pain in Muscular Ischemia, *Arch Int Med* **49** 713 (May) 1932

3 Sutton, D. C., and King, W. B. *Proc Soc Exper Biol & Med* **25** 842, 1928

4 Pearcy, J. F., Priest, W. S., and Van Allen, C. M. *Am Heart J* **4** 390, 1929

5 Sutton, D. C., and Lueth, H. C. Pain, *Arch Int Med* **45** 827 (June) 1930

6 Sutton, D. C. *J Iowa M Soc* **20** 57, 1930

7 Singer, R. *Wien Arch f inn Med* **13** 157, 1926

acute ischemia of the heart could be produced without causing painful reactions. His observations may be objected to, however, on the ground that he used animals with the chest open, anesthetized lightly with morphine, which may have dulled the responsiveness of the animals to the stimulus of ischemia. The further observation that pain responses obtained on compressing the coronary artery depended on a functionally intact adventitia does not preclude the possibility of ischemia causing pain responses. Sutton and Lueth recognized that injury to the pain fibers in the adventitia would prevent transmission of the pain responses.

In the course of an investigation of the pathways taken by such affective stimuli, we had occasion to repeat some of the experiments of Sutton and Lueth and were surprised to find that the responses reported by these investigators did not always occur, which apparently confirmed Singer's results. Consequently, we resolved to investigate the discrepancy further. The results of the study are the subject of the present report.

#### PROCEDURE

In the early experiments, the method used by Sutton and Lueth was followed with few modifications. Each dog was placed, without previous medication, under intratracheal ether insufflation, and the chest was opened anterolaterally in the fifth left intercostal space. On retraction of the ribs, a good exposure of the pericardial sac was obtained in the region of origin of the anterior ramus descendens of the left coronary artery. This artery was dissected out after the pericardium was opened, and a loose ligature was passed beneath the vessel. A second ligature was inserted so as to enclose some myocardial and epicardial tissue, free as far as ascertainable from visible blood vessels. A permanent pericardial fistula was made by fastening to the pericardium a flanged and ridged glass tube, 10 cm in length and 1 cm in diameter. The two ligatures were passed to the outside through this tube, and the parietal wound was closed around one of the ridges in the glass tube. Negative intrathoracic pressure was restored by suction through a small opening in the pleura or by distending the lungs, leaving a small opening in the chest. When the pressure in the chest had approximately returned to the normal level, the small opening in the chest was closed and the dog permitted to breathe naturally. A period of from about two to four hours was permitted to pass in order to give the animal sufficient time to recover fully from the effects of the anesthesia and operation. At this time the dog walked about, appeared comfortable and responded to command. The animal was then placed on the right side. After a minute or so observations were made of the effects of traction on the ligature around the artery sufficient to occlude the vessel. As a control the effect of traction on the myocardial ligature was also noted.

Later the technic was modified in order to bring the cardiac field into the direct view of the observer and to insure the complete closure of the blood vessel, unaccompanied by displacement of the heart. The inability to make these checks, in our opinion, vitiated somewhat the value of the results obtained with the earlier method. For this purpose we substituted a wider glass tube, the inside diameter of which was 5 cm (fig 1). Each of the ligatures employed was passed through a second glass tube, 4 mm in diameter, to prevent tangling with other ligatures and to permit controlled compression of the blood vessels

or of the myocardium without displacement of the heart. The smaller tubes are omitted in the figure for the sake of clarity.

The objective criteria used to show the presence of a positive affective response were the appearance of the following reactions in a dog which had been resting quietly prior to the stimulus.

1 Quivering and stiffening of the forelimbs, especially of the left, with a latent period of five seconds or less, occasionally accompanied by similar phenomena in the hindlimbs. This sign was present in 95 per cent of the positive responses.

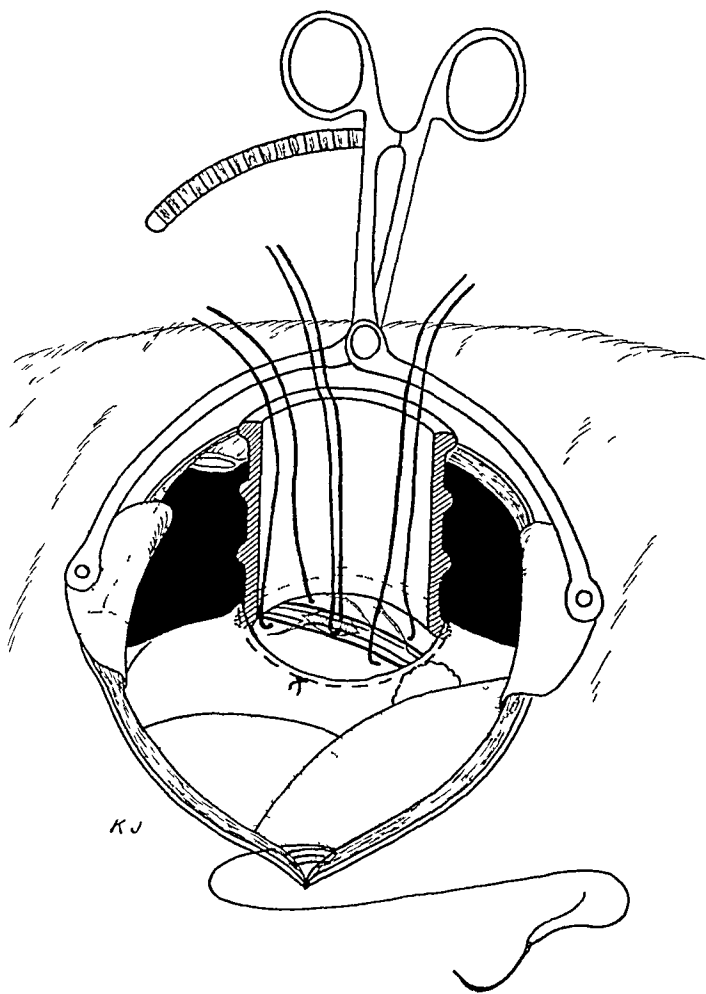


Fig 1—Diagrammatic representation of the improved operative procedure, just before closure of the anterior thoracic wall.

2 Sudden restlessness with movements of the head and attempts to stand up. These phenomena occurred with a latent period of from one to fifteen seconds in 100 per cent of the positive results.

3 Sudden increase in the rate and in the depth of respirations, accompanied by whining or barking. This occurred in 50 per cent of the positive responses.

5 Salivation and retching. This reaction occurred in 50 per cent of the positive responses.

The positive responses when the cardiac ligatures were pulled differed from the response obtained on compressing a somatic sensory nerve only in the

mability of the animal to locate the site of irritation. The responses were labeled roughly 0, when no positive response was obtained, and +, ++, +++ and +++++, depending on the degree of the reaction.

### RESULTS

The results of the experimentation are tabulated diagrammatically in figures 2 to 8. The figures illustrate the summation of the results of a number of trials of each procedure. Traction on each ligature was repeated several times at intervals of from two to five minutes. Traction was maintained for from one second to thirty seconds depending on the response. Often occlusion of the vessels led to cardiac dilatation and

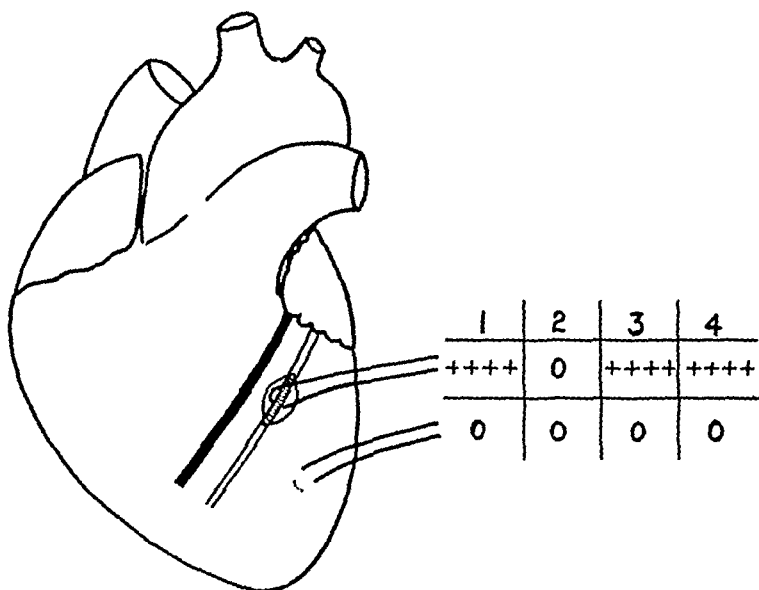


Fig 2—Diagrammatic representation of the results obtained in animals 1 to 4. A positive response was obtained in animal 2 on stimulation of a somatic nerve.

slowing. The artery was often dilated above and considerably narrowed below the constriction. The myocardial region supplied by the artery showed a distinct paling compared with the rest of the heart.

### COMMENT

In the preliminary experiments (fig 2) it was found that in three of four animals a definite positive affective response was obtained when the coronary artery was occluded. In the fourth instance (experiment 2) a negative response was obtained, although the stimulation of a somatic nerve gave a definitely positive response.

In the next group of animals (experiments 5 to 9, fig 3), a third ligature was placed in addition to the two previously used. This ligature was passed by means of a curved needle beneath a minor branch of



the ramus descendens and its accompanying vein, located cephalad to the region where the artery had been dissected free. Care was taken to include the tissue surrounding the vessels in this ligature. This additional ligature was used in order to determine whether or not the occasional absence of pain might be due to the interruption of the afferent nerve pathways responsible for the affective response. In this group of experiments traction on the two coronary ligatures, that on the dissected and that on the undissected artery, gave positive responses except in the case of animal 6. This animal, however, was found to be unresponsive to somatic stimulation as well.

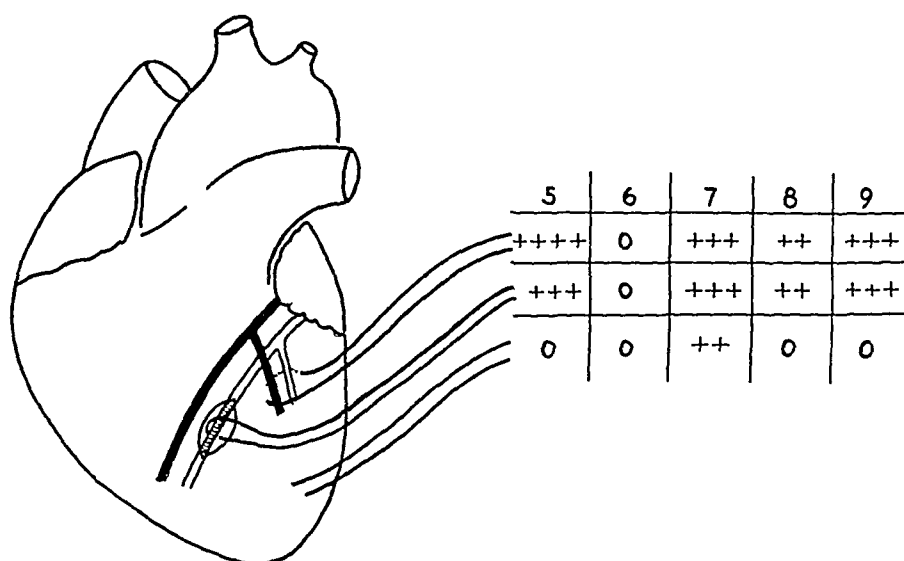


Fig 3—Diagrammatic representation of the results obtained in animals 5 to 9. A negative response was also obtained in animal 6 on stimulation of a somatic nerve. A large muscular coronary artery was included in the control myocardial ligature in animal 7.

Incidentally, animal 7 is the only one of our fifteen animals in which a positive affective response was obtained by compressing the myocardium by traction on the control ligature. In this animal autopsy revealed that an intramuscular coronary artery of considerable size had been included in the ligature. In none of the other animals did an affective response result from traction on the myocardial ligature.

In the case of animal 10 (fig 4) the procedure was again modified in that two ligatures were passed under the ramus descendens close to each other with no branches intervening. The region enclosed by the lower ligature was painted with phenol and alcohol during the operation. It was found that when the animal recovered traction on the upper region gave a positive response whereas that on the lower did not. For animal 11 (fig 4) a similar placement of ligatures was employed,

but neither region was painted with phenol and alcohol. Traction on each of these regions gave a positive response. This positive response disappeared in the case of traction on the lower ligature after the region enclosed by it was painted with phenol and alcohol, traction on the upper ligature still gave a positive response.

The foregoing results suggested to us that (1) the absence of a positive affective response was not due to the interruption of afferent pathways, (2) the positive response was due to the compression of afferent fibers enclosed within the sheaths of the coronary vessels, and (3) occlusion of the coronary vessels by the ligature and the consequent

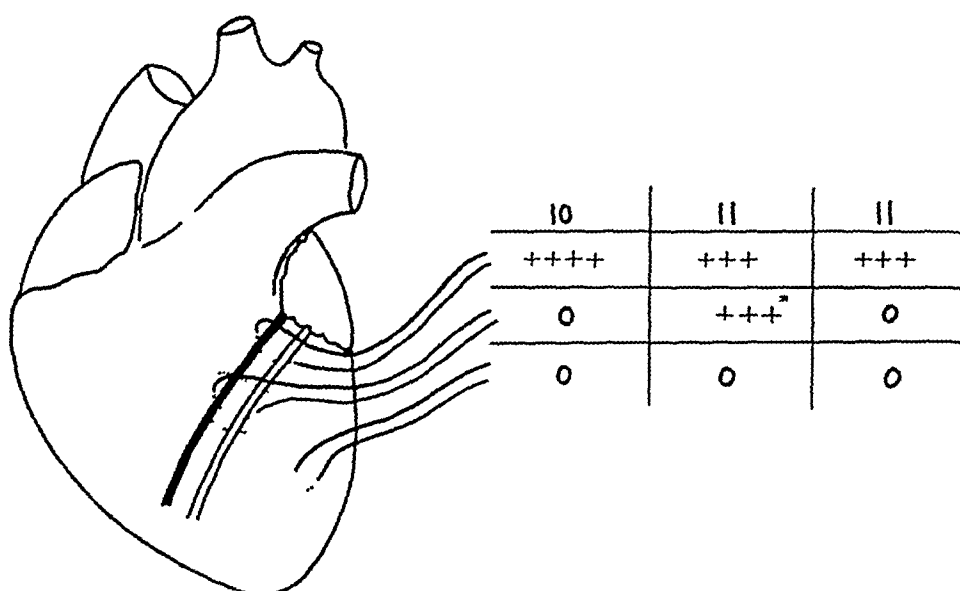


Fig 4—Diagrammatic representation of the results obtained in animals 10 and 11, showing the effect on the affective response of destroying the nerve plexus. The asterisk shows the results obtained with animal 11 on traction of area enclosed by dotted line before painting with phenol and alcohol.

change in the flow of the blood did not produce the affective response. To test this conception we modified our technic further. In the first place, we carefully cut down on the artery to be dissected, gently separated it from the sheath and then carefully stripped off the adventitial coat for a distance of 1 cm. The ligature was then placed beneath this dissected region. In this way we hoped to denervate the dissected strip completely without destroying the afferent pathways from more distal regions. This, we thought, was possible because the sensory nerves of the coronary arteries, like those of other arteries, course along the sheath and the adventitia of the vessel in a loose network and at intervals send down branches to the muscular coat. In the second place we passed a ligature around the undissected vessels not only above but below the dissected region. We expected to find, if our

concept was correct, that the compression of the artery at the point of dissection would elicit no affective response, whereas compression above and below would elicit a positive response if the afferent pathways were still intact. In the two animals, 12 and 13 (fig 5), in which this test was made the results obtained were as anticipated.

At the termination of the experiment on animal 13, the coronary vessels were occluded by a hemostat, which at postmortem examination was shown to have completely occluded the ramus descendens and its accompanying veins. Although the hemostat was kept in place for twenty minutes before the animal was killed, it caused no positive response except momentarily when it was applied. However traction

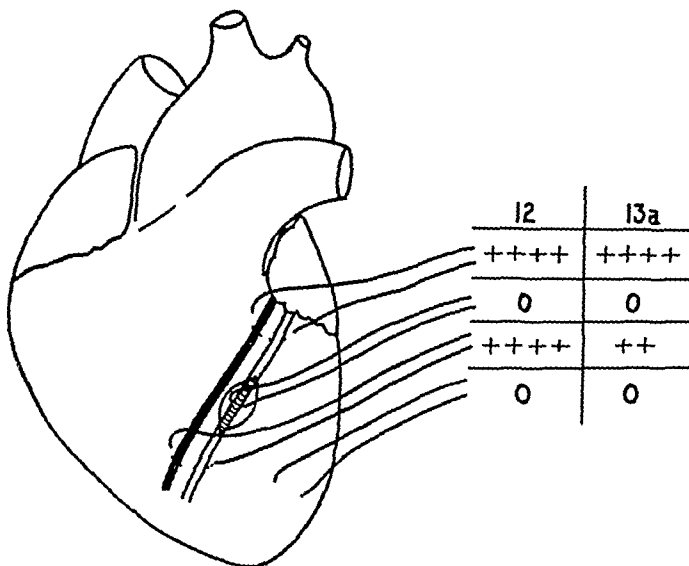


Fig 5—Diagrammatic representation of the results obtained in animals 12 and 13, showing the effect of dissection of the sheath and adventitia of the artery on the affective response.

on the ligature above the occlusion repeatedly produced a positive response (fig 6).

In order to rule out the possibility that the difference between the result of traction on the ligature in the dissected and that in the undissected region was due to the absence of occlusion of the accompanying veins in the case of the dissected artery, the procedure used with animals 12 and 13 was repeated with animal 14, with the additional modification that the vein as well as the artery was dissected free and a ligature placed beneath this vessel also. As shown in figure 7, no affective response was obtained when both the artery and the vein were occluded at the site of dissection, at the same time positive responses were obtained from compression by traction of the other ligatures on the vessels above and below this point.

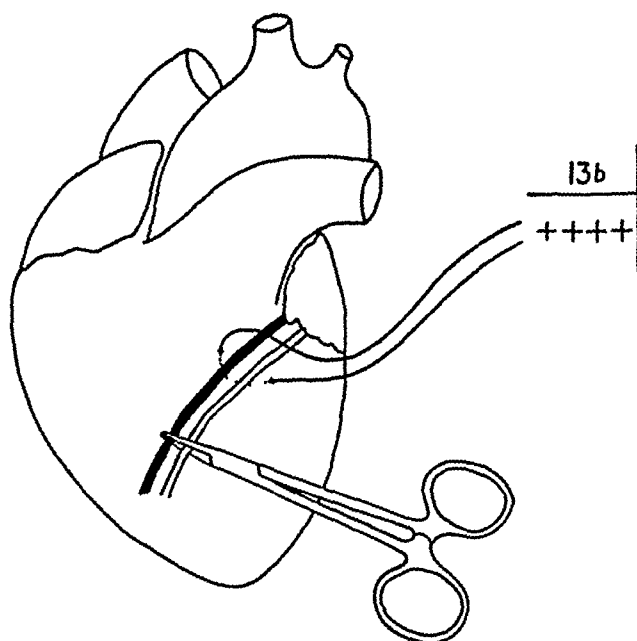


Fig 6—Diagrammatic representation of the results obtained in animal 13, showing the effect of traction above the site of complete coronary occlusion

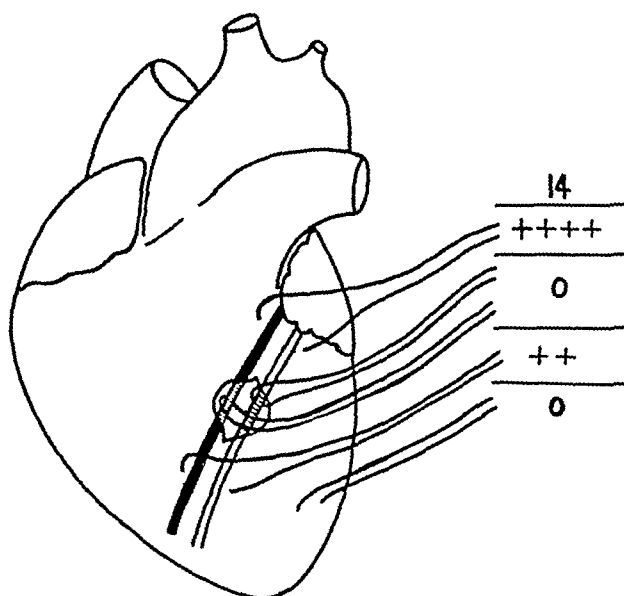


Fig 7—Diagrammatic representation of the results obtained in animal 14, showing the absence of effect of occlusion of the carefully dissected artery and vein on the affective response

As a final check, in the case of animal 15 (fig 8) the ramus descendens was carefully dissected out and then tied off completely (The occlusion was checked by postmortem examination) Ligatures were passed under the coronary vessels above and below in such a way that no branches came off between the ligatures By traction on the ligatures after the animal had recovered from the anesthesia affective responses were obtained even though the artery was already occluded

All of these results, it seems to us, indicate that the positive affective response is due not to occlusion of the coronary artery and interference with the flow of blood within it but rather to the direct stimulation of afferent fibers in the nerve plexus surrounding the coronary vessels

The objection may be raised that insufficient time may have been allowed for the development of ischemia in view of the possible col-

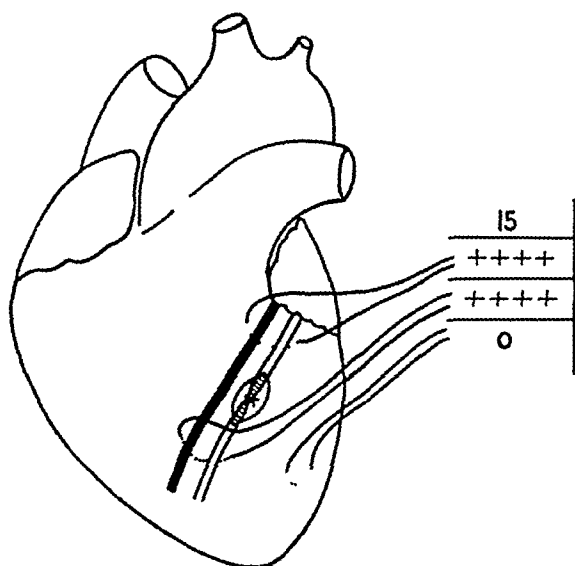


Fig 8—Diagrammatic representation of the results obtained in animal 15, showing the effect of traction above and below the site of complete coronary occlusion

lateral supplies The results obtained with animal 15 are opposed to this view, since the ligation of the vessel was maintained over a period of hours Furthermore, in several of the animals ligation of the coronary arteries without interruption of the afferent pathway was performed at the end of the experiment without causing any affective responses, even though the occlusion was maintained for as long as half an hour Deliberate rupture of the coronary vessels at the point of dissection with consequent interruption of the blood supply to the heart muscle caused no affective response, even though the animal eventually became unconscious and previous tests had shown that the afferent pathways were intact The addition of a pericardial tamponade in the animals last mentioned by closing off the pericardial cannula hastened

the occurrence of unconsciousness from which the animal quickly recovered when the pressure in the pericardial sac was relieved. In no instance did a pericardial tamponade lead to affective responses, although there can be no doubt that the heart was quickly rendered ischemic.

In conclusion, we are of the opinion that the experimental data indicate that, at least in the dog, a coronary artery, such as the anterior ramus descendens, may be suddenly and completely occluded without causing pain, even if care is taken to leave the sensory pathways intact. Further, the cardiac pain observed by Sutton and Lueth,<sup>5</sup> Peaicy, Priest and Van Allen,<sup>4</sup> White, Garrey and Atkins,<sup>8</sup> and others in dogs is not the result of cardiac ischemia but is due to direct mechanical stimulation of the afferent nerves.

#### THEORETICAL CONSIDERATIONS

It is definitely established that the coronary arteries, like most arteries, have sensory endings in the adventitial coat, an observation first made by Dogiel.<sup>9</sup> Woollard<sup>10</sup> recently pointed out that the nerves to and from the ventricles are concentrated for the most part around the coronary blood vessels, where they form a loose spiral network (fig. 9). The afferent fibers from the end-organs in the artery join this plexus, at first, however, running in intimate contact with the artery. The absence of pain fibers in the rest of the myocardium, first shown by Harvey, has been confirmed many times in man and in the lower animals. It appears, then, that the pain fibers, as our study also shows, are confined to the plexus in the neighborhood of the coronary vessels. The work of Woollard<sup>10</sup> has clearly demonstrated that the nerves from the ventricles congregate for the most part around the mouths of the coronary arteries before passing over to the aortic plexus. It is not unlikely that the pain responses obtained by Sutton and Lueth<sup>5</sup> in probing the mouths of the coronary arteries were due to the stimulation of this nerve plexus rich in pain fibers and not directly to the occlusion of the mouths of the arteries. It is indeed possible that even sudden death, the result of ventricular fibrillation, might have been caused by reflex or by direct nerve stimulation.

The absence of evidence in our experiments that myocardial ischemia leads to pain in the dog and the deduction from our experiments and those of Singer<sup>7</sup> that presumably it does not produce pain responses

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<sup>8</sup> White, J. C., Garrey, W. E., and Atkins, J. A. Cardiac Innervation, *Arch. Surg.* **26**: 765 (May) 1933.

<sup>9</sup> Dogiel, A. S. *Arch. f. mikr. Anat.* **52**: 44, 1891.

<sup>10</sup> Woollard, H. H. Innervation of the Heart, *J. Anat.* **60**: 345, 1926.

should not be taken to indicate that myocardial ischemia plays no rôle in man. In the first place, it must be borne in mind that the presence of a rich anastomosis of blood vessels in the dog may prevent the development of a sufficient degree of ischemia such as occurs in man. Further-

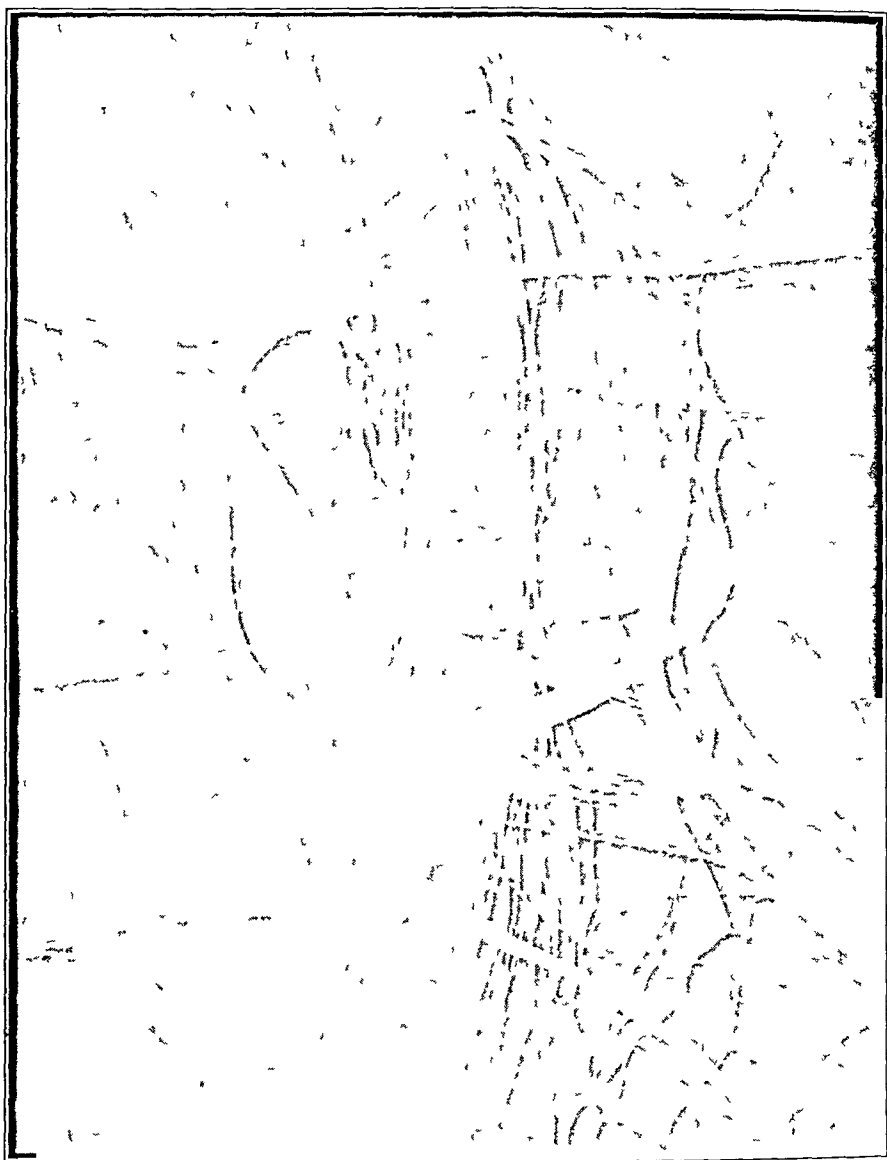


Fig 9—Network of nerves surrounding a small coronary artery (from Woollard<sup>10</sup>)

more, it is not unlikely that the threshold to painful stimuli may be considerably higher in the dog than in man.

Nevertheless, our work has served to emphasize the importance of the nerve fibers and nerve endings in the production of pain. The absence of sensitivity to pain in the heart muscle and the concentration of the sensory end-organs around the blood vessels make it seem likely

that if ischemia causes pain it does so by acting as a stimulus on the end-organs located in the region of the coronary vascular tree. This might take place by diffusion of the pain-producing substance or substances from the myocardium to the end-organs located around the blood vessels, especially the smaller ones, or by a concentration of the pain-producing substance formed locally. In fact such a concentration might be aided in certain instances by the accumulation of pain-producing substances in the blood supplying the coronary arteries as a result of ischemia throughout the rest of the body.

The stimulation of the nerve endings need not be merely chemical. Sudden rises in blood pressure, such as may occur in exposure to cold, in sudden emotional upsets and strains or during dreams and the like, by distending the coronary arteries may mechanically stimulate the many nerve endings located in the walls and give rise to an attack of pain. Furthermore, the direct action of the arteriosclerotic process in the coronary vessels as it spreads to the adventitia or is accompanied by periauterial changes may render the nerve endings within the walls at first hyperirritable and later by destruction, insensitive to stimulation. These changes would most certainly alter the responses. In the state of hyperirritability, stimuli which would ordinarily not affect the pain endings might readily do so and give rise to an anginal attack. This fact may be the crux in the difference in response to similar circulatory disturbances between normal persons and those with coronary disease.

It must further be borne in mind that during the process of involvement of the nerve endings and also the nerve fibers in the adventitia the actual advance of the pathologic process may by itself give rise to painful attacks as successive groups of fibers and endings are first stimulated and then destroyed. Infarction may operate in exactly this way on the nerve endings and nerve fibers present in the infarcted area.

From these considerations, it seems clear that ischemia may be only one of many mechanisms which can give rise to attacks of cardiac pain. Others operating alone or in summation with ischemia may also be important. But all of these mechanisms must operate by stimulating the nerve endings for pain or the afferent nerve fibers propagating pain. The condition of this nerve apparatus is therefore of vital importance in the mechanism of the production of pain.

Our work casts no light on the possibility of similar actions on the pain endings and afferent pain fibers of the aorta, except that a process in the aorta similar to that in the coronary arteries is highly probable. It is further possible that under certain circumstances there may be a summation of the effect of the two regions.



## SUMMARY AND CONCLUSIONS

The observation of previous workers is confirmed that occlusion of the coronary vessels and the surrounding tissue in the unanesthetized dog gives rise to an affective response resembling an anginal attack. The response from this procedure is similar to that obtained on compressing a superficial somatic sensory nerve, save for the inability of the animal to locate the site of irritation.

Our results show that this response is due not to the occlusion of the coronary artery but to stimulation of afferent fibers located in the nerve plexus surrounding the vessels. The evidence for this is

1 Occlusion of a carefully isolated strip of the coronary artery caused no response, but a definite response was obtained when the undissected coronary vessels above and below this point were compressed.

2 Destruction of the nerve plexus with phenol and alcohol abolished the response to compression, but the response was still positive when a region above the phenolized area was stimulated.

3 Complete preliminary occlusion of the carefully isolated coronary artery did not prevent a positive response to compression above or below this point.

4 Pericardial tamponade following bleeding from a ruptured coronary artery caused syncope but no "anginal" response.

Positive affective responses occur only when the region about the coronary vessels is compressed. The rest of the myocardium and epicardium is insensitive to stimulation by pressure.

It is concluded that ischemia of the myocardium is at most one of many mechanisms operating on the nerve endings and nerve fibers which may give rise to anginal attacks.

# MUSHROOM POISONING (MYCETISMUS)

## REPORT OF FOUR CASES

JOSEPH B VANDER VEER, M D

AND

DAVID L FARLEY, M D

PHILADELPHIA

From the earliest time mushrooms have been eaten by the people of many countries. The ancient Babylonians and early Romans employed them as a food and delicacy. For centuries they have been sold in the public markets of the larger cities of Europe and Asia. The earliest recorded instance of mushroom poisoning is that which occurred in the family of the Greek poet Euripides (fifth century, B C). Euripides' wife, two sons and a daughter died from this cause. The Latin historian Pliny related that deaths from mushroom poisoning were not uncommon in ancient Rome, and mentioned the names of several prominent men, including a pope and two emperors, who lost their lives in that way. This period has been termed the "golden age of poisonings," and one wonders whether all these deaths were entirely accidental.<sup>1</sup>

Paulet<sup>2</sup> was the first to study seriously the subject of mushroom poisoning. He stated that in the vicinity of Paris alone from 1749 to 1788 there were at least one hundred deaths from this cause. During the latter part of the past century there have been many studies and reports on this subject, especially from France. In America the first cases were reported by Cheney in 1871.<sup>3</sup> After that cases were reported from all parts of the United States. There is now an extensive literature on the subject, especially in the French and German languages. During the past two decades, however, only a few clinical pathologic studies on mushroom poisoning have been reported in English and none has included complete studies on the pathologic changes in the central nervous system. The textbooks on general medicine and the various systems of medicine, with a few exceptions, dismiss the subject with a few words.

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From the Pennsylvania Hospital

1 For an excellent and complete discussion of mushroom poisoning the reader is referred to the chapter by W W Ford in Peterson F, Haines, W S, and Webster, R W. *Legal Medicine and Toxicology*, Philadelphia W B Saunders Company, 1923. Much of the historical material in this paper has been obtained from that source.

2 Paulet. *Traite des champignons de France*, 1793, quoted by Ford.<sup>4</sup>

3 Cheney, W F. Cases of Mushroom Poisoning, *Pacific M & S J* 5 119 (Aug) 1871.

In the foreign countries where figures are available there has been a marked increase in the incidence of and in the mortality from mushroom poisoning during the past few years. This has been attributed to an increase in the consumption of wild mushrooms coincident with recent depressed economic conditions. It appears probable that a similar condition has obtained in this country.

#### TYPES OF MUSHROOM POISONING

The classification of mushroom poisoning (mycetismus) proposed by Ford<sup>4</sup> embraces all types of poisoning from this cause and has been widely accepted.

1 *Mycetismus Gastro-Intestinalis* —In this type of poisoning violent nausea and vomiting with diarrhea are the only symptoms. Recovery is usually rapid.

2 *Mycetismus Choleraiformis* —Violent abdominal pains followed by nausea and vomiting and usually by profuse diarrhea characterize this type of mushroom poisoning. Severe hepatitis with jaundice is nearly always present. Toxic nephritis and anuria occur frequently. Delirium and coma are frequent terminal symptoms. Poisoning of this type is caused by the many varieties of *Amanita phalloides*. At least 50 per cent of the victims die (fig 1).

3 *Mycetismus Nervosus* —In cases of mycetismus nervosus severe gastro-intestinal symptoms predominate at the outset but are soon accompanied by profuse salivation, perspiration and lacrimation. Giddiness, confusion, delirium, convulsions and coma may occur. The fungi producing this type of poisoning are those containing muscarin or closely related substances and comprise mainly the *Amanita muscaria* group and some belonging to the genera *Clitocybes* and *Inocybes*. The victims are seriously ill, and death occasionally occurs (fig 2).

4 *Mycetismus Sanguinarius* —In this type of poisoning gastro-intestinal symptoms occur at the onset, later there is rapid hemolysis, causing anemia, jaundice and hemoglobinuria. The mortality is low.

5 *Mycetismus Cerebralis* —Transient excitement, hallucinations and dilatation of the pupils are present in cases of mycetismus cerebri. Collapse may occur. Recovery generally takes place.

Many of the varieties of poisonous fungi causing mycetismus of types 1, 4 and 5 are uncommon in America, and as the symptoms are often relatively mild and fatalities seldom occur, the cases comprising these groups are rarely seen by physicians in the United States.

There are, however, over eighty species of poisonous mushrooms in this country. Of these the genus *Amanita* is responsible for prac-

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4 Ford, W. W. A New Classification of Mycetismus, Tr. A. Am. Physicians 38: 225, 1923.

tically all the severe cases of mycetismus. The most deadly species, *Amanita phalloides*, causes over 90 per cent of the deaths from mushroom poisoning. Some of the remaining fatalities are due to *Amanita muscaria*. These two species are extremely common in all parts of this country. They thrive from early June till the first frosts. The flavor

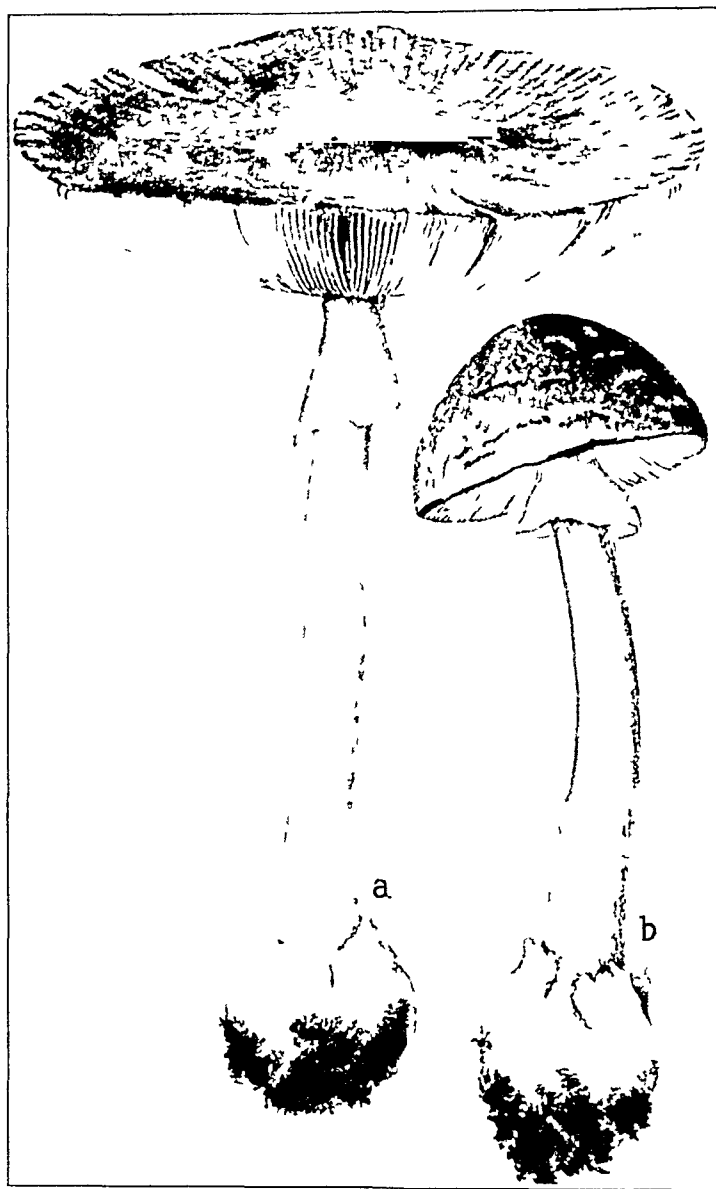


Fig 1—Specimens of *Amanita phalloides*, a deadly poisonous mushroom (From the 'Yearbook of the United States Department of Agriculture,' 1897.) An adult specimen (*a*) and a young specimen (*b*) is shown in the illustration.

of *Amanita phalloides* is said to be delicious. The young specimens are the most poisonous and are also most apt to be mistaken for the edible forms by the inexperienced mycologist. Other persons, even less judicious, may ingest poisonous varieties after trying various "tests" on them. One of the favorite tests consists in placing a piece of bright

silver in the utensil while the plants are cooking. If the silver is not tarnished, the mushrooms are considered safe for consumption. The efficacy of this test is believed in by an astounding number of people.

It is not within the province of this paper to deal with the botanical characteristics of mushrooms. It is always desirable to identify the type of poisonous fungus responsible for the illness, but in practice this can

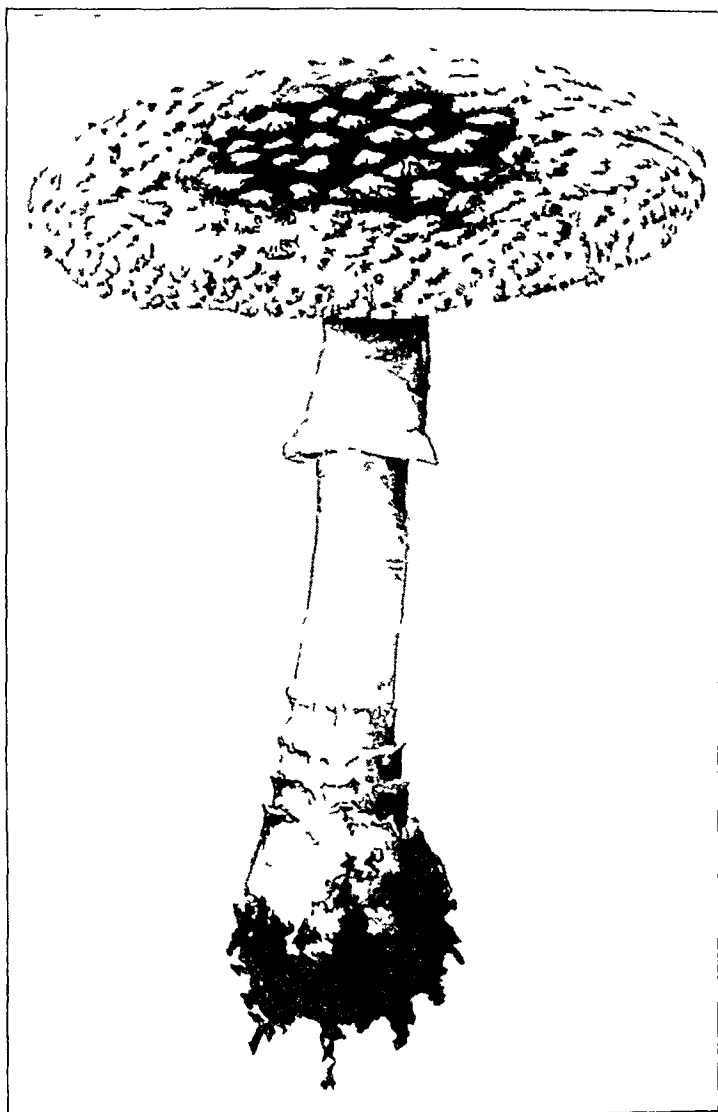


Fig 2—Adult specimen of *Amanita muscaria*, a poisonous mushroom (From the "Yearbook of the United States Department of Agriculture," 1897)

seldom be done in time to be of value in treating the condition. Often there are no remaining specimens on which to pass judgment, and if there are, a competent mycologist is rarely available. Thus the physician is left with the history and clinical picture on which to base the diagnosis and therapy.

In this country the two types of severe mushroom poisoning which are apt to be encountered are (1) the rapid type (*mycetismus nervosus*) due to *Amanita muscaria* and (2) the delayed type (*mycetismus choleriformis*) caused by the various forms of *Amanita phalloides* (tables 1 and 2)

TABLE 1—*Mushroom Toxins*

	<i>Amanita Muscaria</i>	<i>Amanita Phalloides</i>
Substance	(1) Muscarin (Schmiedeberg, O., and Koppe, R. <i>Das Muskarin</i> , Leipzig, I. C. W. Vogel, 1869) an alkaloidal like substance, the action of which closely resembles that of pilocarpine  (2) Pilz Atropin (Mushroom Atropine) (Kobert, L. R. <i>Lehrbuch der Intoxikationen</i> , ed. 2, Stuttgart, Ferdinand Enke, 1906, p. 1224) and Pilztoxin (Mushroom toxin) (Harmsen, F. <i>Arch f exper Path u Pharmacol</i> 50: 361 [Dec.] 1903)	(1) Amanita Toxin (Ford, W. W. J. <i>Exper Med</i> 8: 437 [May] 1906 Schlesinger, H., and Ford, W. W. J. <i>Biol Chem</i> 3: 279, 1907) thermostable, probably either an indol derivative or an aromatic phenol combined with an amine group  (2) Amanita Hemolysin ("Phallin") (Kobert, E. R. <i>St Petersburg Med Wehnschr</i> 16: 463 [Dec 21] 1891) thermolabile (70 C) and destroyed by gastric juice
Action	Stimulation of the autonomic nervous system with increased secretion from the various glands, sometimes cardiac and respiratory paralysis	Hemorrhages into the serous membranes and parenchymatous organs, with severe degenerative changes and fatty infiltration of the cardiac muscle, liver and kidneys, the liver often resembling that seen in phosphorus poisoning or acute yellow atrophy, severe degenerative and fatty changes in the cells of the central nervous system
Antidote	Atropine, nearly a perfect physiologic antidote	

TABLE 2—*Mushroom Poisoning*

	Rapid Type	Delayed Type
Causative Agent	<i>Amanita muscaria</i> group	<i>Amanita phalloides</i> group
Onset of Symptoms	From within a few minutes to three hours after ingestion	From six to fifteen hours after ingestion
Symptoms	Excessive salivation and lacerimation, pupils contracted and not reacting to light or in accomodation nausea and vomiting, abdominal pains with profuse watery evacuations, pulse at times slow and often irregular, dizziness and confusion with convulsions and coma in severe cases, fatal cases, death within a few hours	No symptoms for several hours, on set sudden with severe abdominal pains, nausea, vomiting, and usually diarrhea, vomitus and stools often showing blood and mucus, extreme thirst, anuria at times, usually jaundice in from two to three days, cyanosis and coldness of the extremities, increasing prostration with coma and death, fatal cases, death usually from fifth to eighth day
Prognosis	Good in mild cases good in severe cases if patient is treated with atropine	Grave mortality, from 50 to 70 per cent, often 100 per cent of a group

## POISONING DUE TO AMANITA PHALLOIDES

The opportunity to follow four cases of poisoning due to *Amanita phalloides* has brought this subject to our attention

On Sept 16, 1932, two Italian families, who were employed by a farmer near Trenton, N. J., gathered a large number of mushrooms from a nearby wood

To make certain that the plants were not of a dangerous variety, a silver quarter was placed in the pan while they were being prepared. It did not become tarnished. About 7 p. m. the adults of both families (two men and two women) each ate a large helping of the cooked mushrooms.<sup>5</sup> The flavor was excellent, and no untoward symptoms were noted during the evening.

At about 2 a. m. (seven hours after supper) one of the women was awakened by severe abdominal pain. Nausea, vomiting and marked purgation soon followed. Dizziness and extreme prostration were present. At about 4 a. m. her husband's suspicion that the mushrooms eaten might have been poisonous was aroused. Although he felt no ill effects at that time he took about 2 ounces (62.2 Gm.) of magnesium sulphate (the entire household supply). A physician who was called at about 6 a. m. administered an emetic and  $\frac{1}{50}$  grain (0.0013 Gm.) of atropine hypodermically to the ill woman. The other man was beginning to note abdominal pains at that time and was given similar medication. The man who had taken the magnesium sulphate and the remaining woman were not treated at this time. At about 10 or 11 a. m. they also became ill. During the next thirty-six hours all were extremely prostrated by severe abdominal pains, profuse diarrhea (not bloody) and severe retching and vomiting. Jaundice was noted after forty-eight hours in all the patients. The first woman was nearly moribund on the third day, while her husband (the man who had taken the magnesium sulphate) was the least ill. The other couple were extremely weak, but the vomiting had stopped and the diarrhea was subsiding. Against their physician's advice the patients were brought to Philadelphia by automobile, a distance of over 50 miles. Abdominal pains with nausea and vomiting returned, and by the following day the patients were more jaundiced and were again extremely ill. They were brought to the Pennsylvania Hospital on September 20, the fourth day after they had eaten the mushrooms.

#### REPORT OF CASES

CASE 1—A. P., a woman aged 26, was admitted to the medical service of Dr. Arthur Newlin on Sept. 20, 1932. The family, social and past medical histories were irrelevant. Examination revealed a small, swarthy, extremely ill woman. The general development and nourishment were fair. She was drowsy, and it was difficult to hold her attention, though her mind was clear. She complained of nausea, abdominal cramps and marked weakness. Vomiting was attempted several times without success. The sclerae were moderately jaundiced. While the ocular movements were being tested the patient complained of blurring of vision and dizziness, but no ocular palsies were noted. The pupils were small but reacted to light (morphine had been given a few hours before). There was an odor of acetone to the breath. Dental caries and pyorrhea were marked. The tongue was dry and covered with a brownish coat. Sordes was present about the lips and teeth. There was no adenopathy. The lungs were clear to percussion and auscultation except for an occasional moist râle at both bases posteriorly. The heart showed a diffuse apical impulse perceptible in the fourth and fifth left interspaces. Percussion disclosed the left border of the heart 9 cm. from the midline in the fifth intercostal space (midclavicular line, 7.5 cm.). The right border was 2.5 cm. from the midline. The heart sounds were well heard. No murmurs were present. The rhythm was regular, and the rate was 152 per minute. The blood pressure was 80 systolic and 40 diastolic. The abdominal contour was flat. On palpation there was tenderness over the entire abdomen, but it was most

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5 Mushrooms obtained from the same area of the woods and identified by the survivors as the kind eaten proved to be *Amanita phalloides*.

marked over the right upper quadrant. The liver was greatly enlarged its edge reaching to the level of the umbilicus. The surface was smooth and tender on pressure. The spleen was not felt. The extremities were normal except that no tendon reflexes were elicited. The temperature on admission was 99.6 F.

*Course*—The patient was given 10 per cent dextrose in physiologic solution of sodium chloride (850 cc) intravenously shortly after admission, and this was followed by some immediate improvement in her general condition. Late in the afternoon and in the evening she was able to take 1,500 cc of fluids by mouth. There was a urinary output of 300 cc. At 4 a. m. the following morning she vomited some of the fluids taken. At that time the blood pressure was 96 systolic and 60 diastolic. The pulse rate was 160 per minute, and the temperature, 100.6 F. From that time on the patient failed rapidly, sinking into a deep coma from which she could not be aroused. She died at 11.30 a. m. the same morning nineteen hours after admission and on the fifth day after ingestion of the mushrooms.

*Laboratory Data*—Urine. The reaction was acid, the appearance, turbid and amber, the specific gravity, 1.018. There were albumin, 3 plus, and sugar, 1 plus (after intravenous administration of dextrose).

*Blood Count*. There were 4,160,000 red cells and 9,500 white cells, with 80 per cent polymorphonuclears (30 per cent filamented and 50 per cent nonfilamented), 14 per cent lymphocytes, and 6 per cent monocytes. The blood smear showed only vacuolation of the polymorphonuclear neutrophils and giant blood platelets.

*Chemical Examination of the Blood*—On admission the sugar content was 51 mg per hundred cubic centimeters, the urea nitrogen, 33.3 mg, and the creatinine, 1.3 mg. The icteric index was 27.9.

*CASE 2*—J. P., aged 36, the husband of A. P. (case 1), was admitted to the medical service of Dr. Thomas McCrae on Sept. 20, 1932. The family history and past history were irrelevant. Examination revealed a well developed and well nourished man, who was extremely apathetic and drowsy. He complained only of abdominal pain. There had been no diarrhea or vomiting on the day of admission. The urine was scanty and highly colored. He had voided only once on that day. The patient was clear mentally when aroused but answered questions with difficulty, quickly lapsing into a semicomatose state. Jaundice of the skin was evident. The sclerae were jaundiced, and the corneas had a glazed appearance. The pupils were round and equal and reacted well to light. The movements of the eyes were normal. The nose and ears were normal. The lips were dry. The teeth were dirty and the gums infected. The tongue was heavily furred. The peripheral lymph nodes were not enlarged. The lungs were clear throughout to percussion and auscultation. The heart showed no visible or palpable activity. The left border of cardiac dullness was 0.5 cm. outside the left midclavicular line. Over the precordium only the first heart sound was audible, and it was of poor quality. The rhythm was regular, and the rate was 124 per minute. The blood pressure was 85 systolic and 56 diastolic. The abdomen was scaphoid. Hepatic dullness extended 8 cm. below the right costal margin in the midclavicular line. There were rigidity and tenderness to palpation over this area. The edge of the liver was not definitely felt. The extremities were warm, and there was no edema. The tendon reflexes were present and equal but diminished. No petechiae were seen.

*Course*—The patient was given 1,000 cc of 10 per cent dextrose in physiologic solution of sodium chloride intravenously on the afternoon of admission and an equal amount late in the evening. The following morning he was somewhat brighter and was able to take fluids well by mouth. The urinary output was



satisfactory. The abdominal pain was less. There had been no vomiting. The bowels had not moved. The degree of jaundice appeared to be about the same, but the abdomen was less tender. The edge of the liver was easily felt at 4.5 cm below the right costal margin. The blood pressure was 100 systolic and 62 diastolic. On the second morning after admission the patient was decidedly worse. The jaundice was more intense, and the edge of the liver had receded to the costal margin. The patient was unresponsive and could scarcely be aroused. The temperature was normal. The pulse rate was 120 per minute. The blood pressure was 135 systolic and 50 diastolic. Administration of 10 per cent dextrose in physiologic solution of sodium chloride was started by continuous venoclysis, 3,800 cc being given during the next thirty-six hours.

On the third day after admission the patient was deeply comatose. The jaundice was intense. The pupils were dilated and reacted but slightly to light. The temperature was slightly elevated and rose steadily during the day, reaching 107 F. The pulse rate mounted to above 160 per minute and became imperceptible. The respirations were rapid and stertorous. The patient died at 6 p. m. on September 23, seven days after ingestion of the poisonous fungi.

*Laboratory Examination*—Urine. On admission the reaction of the urine was acid, the appearance was clear and amber, the specific gravity was 1.020, there was no albumin and no sugar. Microscopic examination showed from 8 to 10 pus cells per low power field and occasional granular and hyaline casts. On September 23 the reaction was acid, the appearance was clear and amber, the specific gravity was 1.022. There was no albumin, the reaction for sugar was 2 plus (after intravenous administration of dextrose), there was some bile (2 plus), and a few granular casts were noted.

*Blood Count*. The hemoglobin was 95 per cent (Sahli), there were 4,360,000 red cells and 4,950 white cells. The differential count showed polymorphonuclears, 85 per cent, lymphocytes, 14 per cent, monocytes, 1 per cent.

*Chemical Examination of the Blood*. On admission the urea nitrogen content was 42.4 mg per hundred cubic centimeters, the creatinine, 1.5 mg, the chlorides, 516.5 mg. The icteric index was 33.5. On September 22 the urea nitrogen content was 21.7 mg per hundred cubic centimeters, the creatinine, 1.5 mg, the sugar, 104 mg. The carbon dioxide-combining power was 50 volumes per cent. On September 23 the urea nitrogen content was 16.2 mg per hundred cubic centimeters, the creatinine, 1.3 mg, the uric acid nitrogen, 6.7 mg, and the amino-acid nitrogen, 4.3 mg. The icteric index was 71.5.

*Wassermann Test*. The reaction of the blood was anticomplementary.

*CASE 3*—M. M., a white woman aged 29, was the first to become ill (seven hours after she had eaten the mushrooms) and during the first three days was the most prostrated of the four patients. She was considered too ill to be moved and remained at the farmhouse to be cared for by the family physician. Abdominal cramps, diarrhea, nausea and vomiting were severe for four days. After this, anorexia and nausea were present for several days with occasional vomiting and attacks of abdominal cramps. Jaundice appeared on the third day and became deep. During the first week the patient was irrational and in a semicomatose condition a great deal of the time. Prostration was extreme. During the second week improvement gradually occurred, and the jaundice became less marked, though it persisted definitely for over three weeks. Convalescence was slow, but after six weeks the patient was able to do her own housework and complained only of tiring easily. The jaundice had cleared completely, and the general condition was satisfactory.

CASE 4—C M, aged 35, the husband of M M (case 3), suspected that the mushrooms might have been poisonous and took a large saline purge nine hours after eating the fungi. No symptoms appeared (as in case 1) until fifteen hours after ingestion of the mushrooms. Then the patient was seized with abdominal pains, nausea, vomiting and purgation. He was the least prostrated of the four and was able to be up and about part of the time during the first few days and to aid in the care of the other victims. Jaundice occurred but was mild and persisted only a few days. After ten days the patient considered that he had regained his usual health and strength.

NOTE—No salivation, perspiration or lacrimation was present in any of the cases. No blood was noted in the vomitus or feces.

#### NECROPSY OBSERVATIONS

Both necropsies were performed two hours after death by Dr Wayne L Henning and Dr John T Bauer. Examinations of the nerve tissue were made by Dr Bernard J Alpers.<sup>6</sup>

CASE 1 (A P)—The body showed evidence of dehydration. Slight jaundice was present. The peritoneal cavity was not remarkable except that the lymph nodes of the mesentery, retroperitoneum and omentum were prominent. The pleural and pericardial cavities were normal.

*Heart*—The heart weighed 200 Gm. Many small hemorrhages were seen in the epicardium. The valves and heart muscle appeared normal. On microscopic section one area of hemorrhage into the muscle was noted.

*Lungs*—The lungs were normal.

*Spleen*—On gross examination the spleen appeared normal. Microscopically, the pulp spaces were collapsed and showed infiltration with round cells and polymorphonuclear neutrophils.

*Stomach*—The stomach was dilated but was normal in other respects.

*Intestine*—The duodenum was hyperemic, but no hemorrhagic areas were noted. The small and large bowels were free from any areas of hemorrhage or ulceration.

*Pancreas*—The pancreas was normal.

*Liver*—The liver weighed 1,640 Gm. It was dark reddish blue, and the edges were rounded. Cut sections showed that the normal architecture was entirely lost, and areas of hemorrhage and yellowish dots suggested a fatty change. Microscopically, there was a rather uniform destruction of the hepatic parenchyma. Only a few isolated groups of cells immediately about the periportal spaces were well preserved. Considerable fat was present, but the destruction did not seem to be primarily a matter of fatty changes. The outlines of the hepatic cells were lost by swelling, and marked granular changes were present. Nuclear material, detritus and bile pigment were scattered throughout, as were many polymorphonuclear cells. No glycogen could be demonstrated in sections stained with Best's carmine.

*Adrenal Glands*—Round cell infiltration of the medulla and vacuolation of the cells of the zona fasciculata were noted.

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<sup>6</sup> A complete study of the changes in the central nervous system in these two cases was reported by Dr Eli Marcovitz and Dr B J Alpers (The Central Nervous System in Mushroom Poisoning. Report of Two Cases with Toxic Encephalitis, Arch Neurol & Psychiat **33** 53 [Jan] 1935).

*Kidneys*—The kidneys were of normal size. Cut sections showed that the cortex was pale and yellowish. The pyramids were dark and congested. The pelvis and ureters were normal. Microscopically, the epithelium of the convoluted tubules was swollen and granular. The glomeruli showed no acute changes. No glycogen or fat could be demonstrated. The pelvic organs and the bladder were normal.

Microscopically, the aorta, hypophysis, bone marrow and the voluntary muscle tissue were normal.

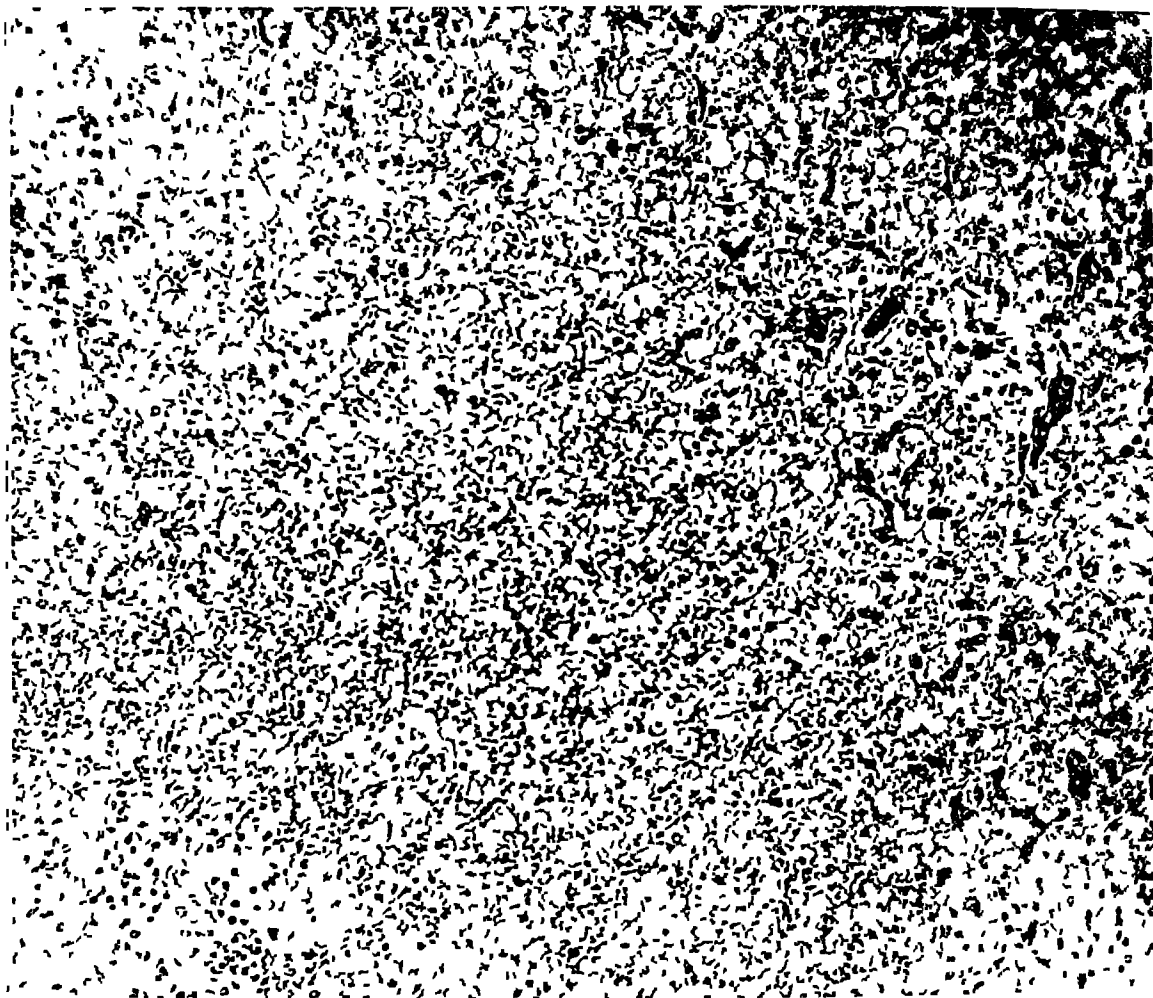


Fig 3 (case 1)—Section from the liver. There is such marked destruction of the parenchymal cells that the section can hardly be recognized as hepatic tissue. Much fat is present, and there are hemorrhagic areas and some cellular infiltration. Magnification,  $\times 140$ .

*Brain*—The brain weighed 1,390 Gm. It was edematous and congested. Scattered punctate hemorrhages were present under the floor of the fourth ventricle and in the midbrain. On microscopic examination the meninges here and there were seen to be filled with blood pigment, red cells, lymphocytes and macrophages. There was a marked loss of ganglion cells in the cortex, especially in the third layer in the frontal and temporal areas. All the ganglion cells in the cortex

showed toxic swelling, and many in the basal ganglions showed similar changes. In the cortex, pallidum and medulla there were areas of perivascular infiltration by lymphocytes. In the medulla there was a focus composed of glia cells, chiefly microglia with some astrocytes. The cortical vessels were mildly thickened, and there was some endothelial swelling. Small punctate hemorrhagic areas were present in the pons under the ependyma of the fourth ventricle. Fat was present in the cortical ganglion cells, cells of the ependyma, astrocytes, microglia and endothelium of the vessels.

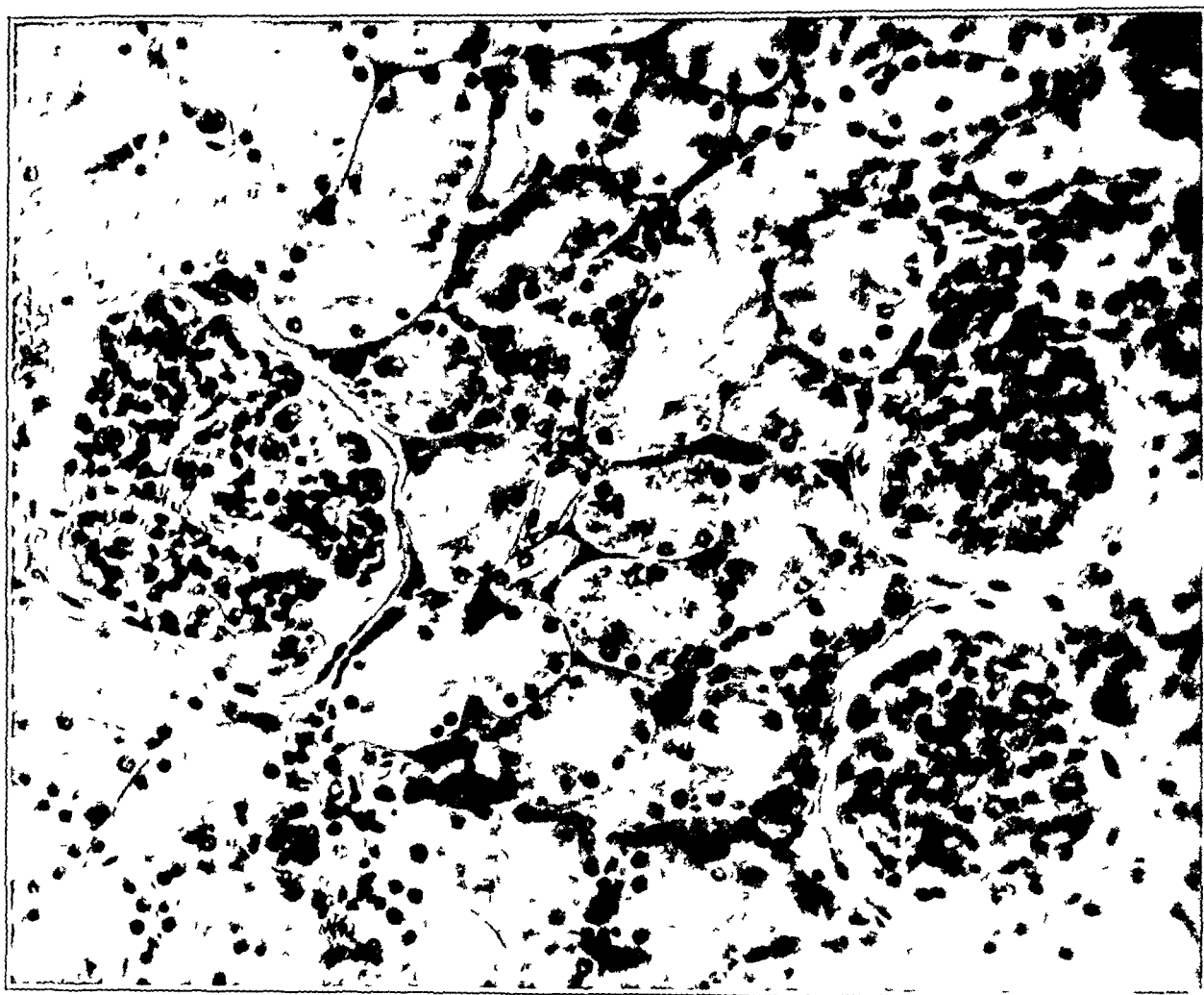


Fig 4 (case 1) —Section from the kidney. Marked degenerative changes are seen in the tubules with little change in the glomeruli and slight inflammatory reaction. Magnification,  $\times 239$ .

CASE 2 (J. P.) —The body was well developed but poorly nourished, and it showed evidence of dehydration. Jaundice of the skin and sclerae was present. The peritoneal cavity showed a small amount of clear fluid. The edge of the liver extended 1 cm. below the costal margin in the right midclavicular line. The right pleural cavity was completely obliterated by an old adhesive process. The left side was normal.

Heart —The heart was of normal size, weighing 250 Gm. The epicardium was smooth. The valves were all normal. Cut sections showed the muscle to be

more pale and slightly less firm than normal. There was no evidence of scarring. Microscopic examination showed scattered hemorrhages throughout the myocardium.

*Lungs*—Grossly and microscopically, there was found only evidence of congestion and edema in the lower half of both lungs.

*Spleen*—Grossly, there was little change. Microscopic sections showed vacuolation of some of the larger cells in the malpighian centers and swelling of the intima in the arterioles in these areas.

*Stomach*—The stomach was normal.

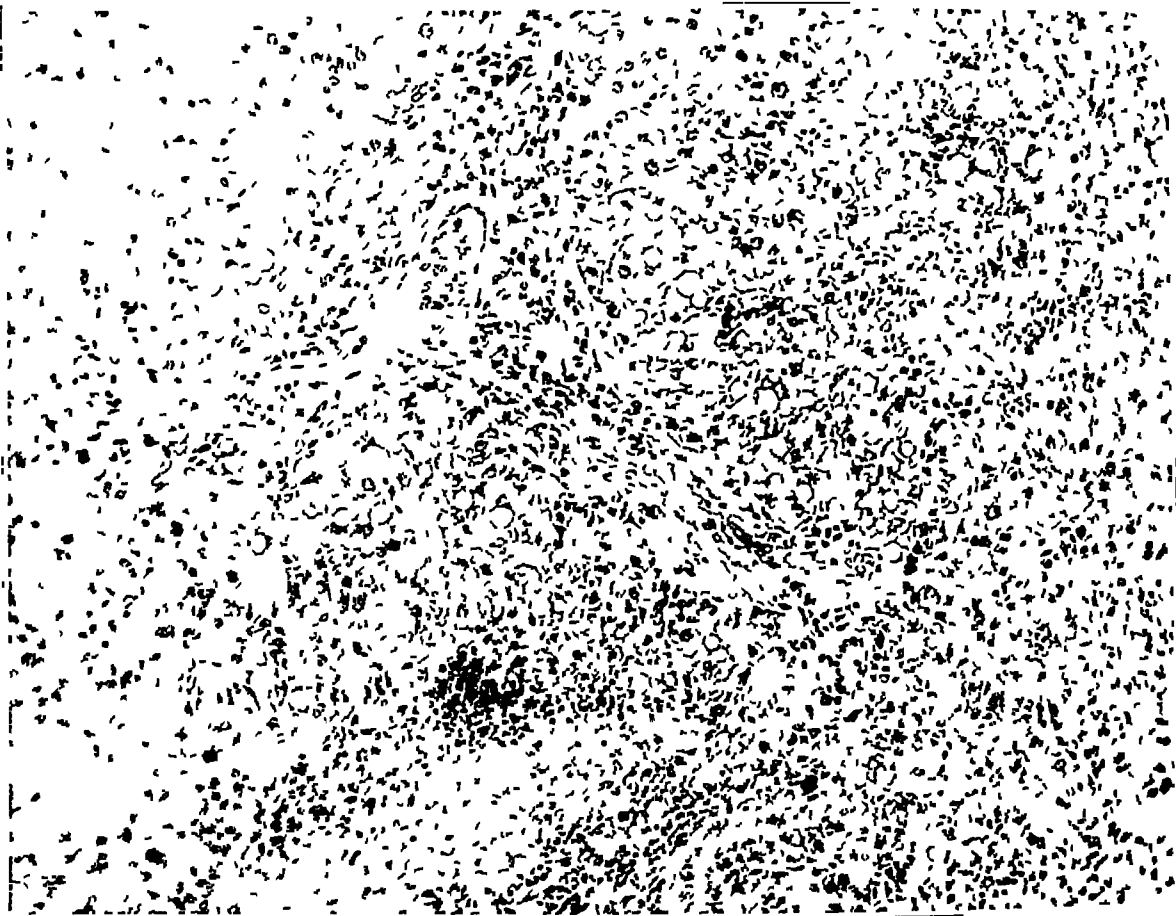


Fig 5 (case 2)—Section from the liver showing a periportal area. The best preserved hepatic cells are seen in these areas. Hemorrhagic areas, fatty change and cellular infiltration with marked destruction of the parenchymal cells are present. Magnification,  $\times 140$ .

*Intestine*—The mucosa of the duodenum was congested and edematous. An increase in the lymphoid content in the lower part of the ileum, some congestion and pinpoint hemorrhagic areas were noted. The microscopic changes were not remarkable.

*Pancreas*—The pancreas was normal.

*Liver*—The liver weighed 1,700 Gm. The surface was smooth and had a mottled yellowish-brown color. The fatty content seemed definitely increased. The cut surface showed a loss of the normal architecture. The gallbladder and large

ducts were grossly normal except for some edema of the wall and mucosa of the gallbladder which was filled with a cloudy mucoid material, without bile. Microscopic sections showed extreme destruction of the hepatic parenchyma. The hepatic cells about the periportal spaces showed the best state of preservation, but even these were altered by swelling and vacuolation, which increased at a distance from these areas until the cells lost their nuclei and became necrotic, vacuolated and pale. Hemorrhagic areas and inflammatory cells constituted a prominent feature, as did fatty changes. Slight regeneration was apparent in some areas.

*Adrenal Glands*—These showed congestion of the medulla with fatty changes in the cortical cells.

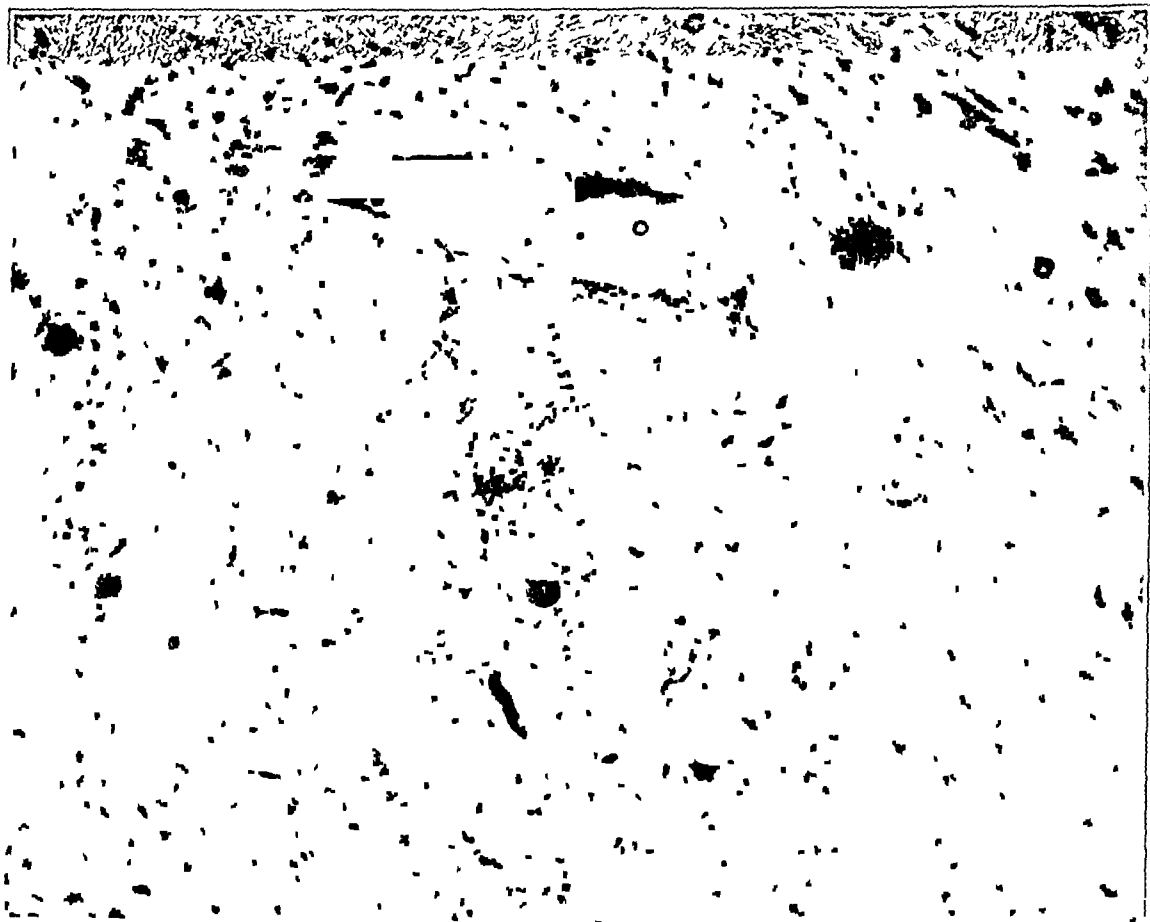


Fig 6 (case 1) —Section from the medulla. An inflammatory focus is shown in the medulla and around a vessel in the immediate neighborhood. Toluidine blue stain,  $\times 115$ .

*Kidneys*—These were normal in size. Swelling and congestion of the cortex were present. Yellowish-gray specks were noted in the areas of the convoluted tubules. The pelvis and ureters were normal. Microscopically, general congestion was present. The epithelium of the convoluted tubules was granular and greatly swollen. Hemorrhagic areas were noted beneath the epithelium of the pelvis.

*Bladder*—Reddening of the trigon area and evidence of hemorrhages beneath the mucosa were noted. Microscopically, hemorrhagic areas were also seen scattered throughout the muscle.

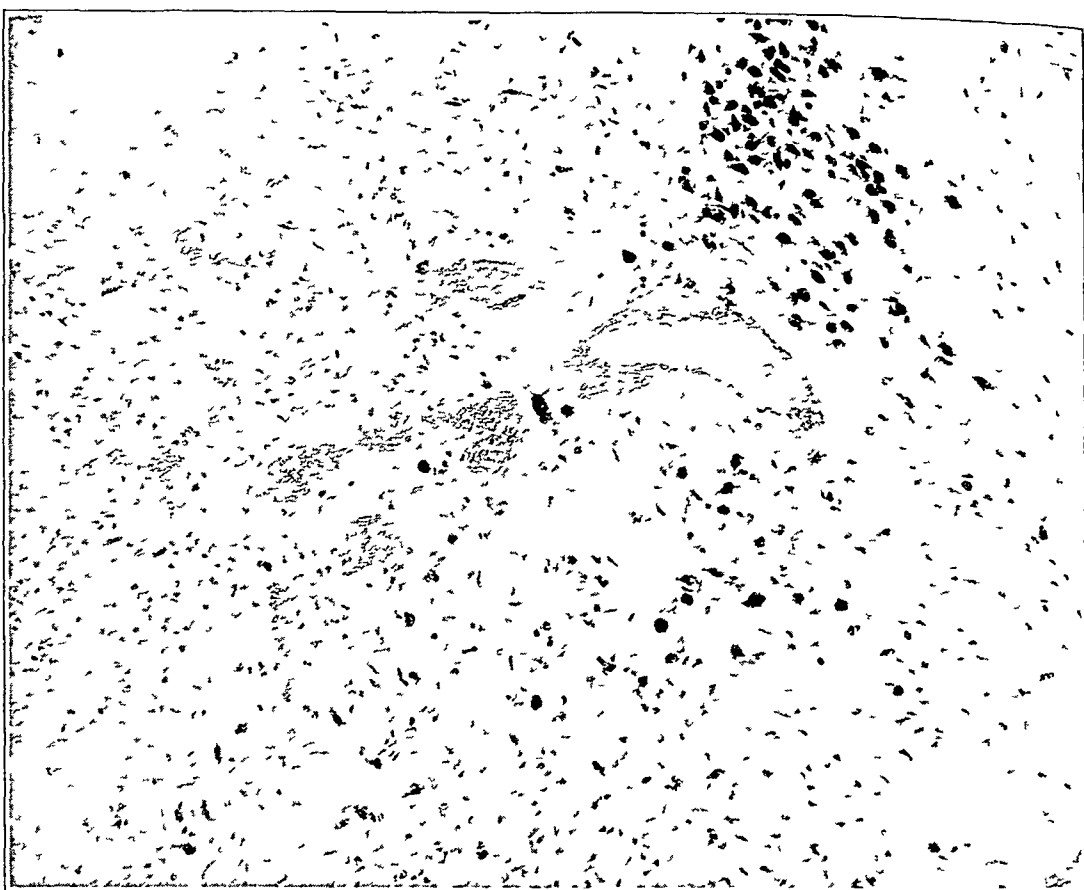


Fig 7 (case 1) —Section from the pons showing punctate hemorrhagic areas under the floor of the fourth ventricle Toluidine blue stain,  $\times 138$

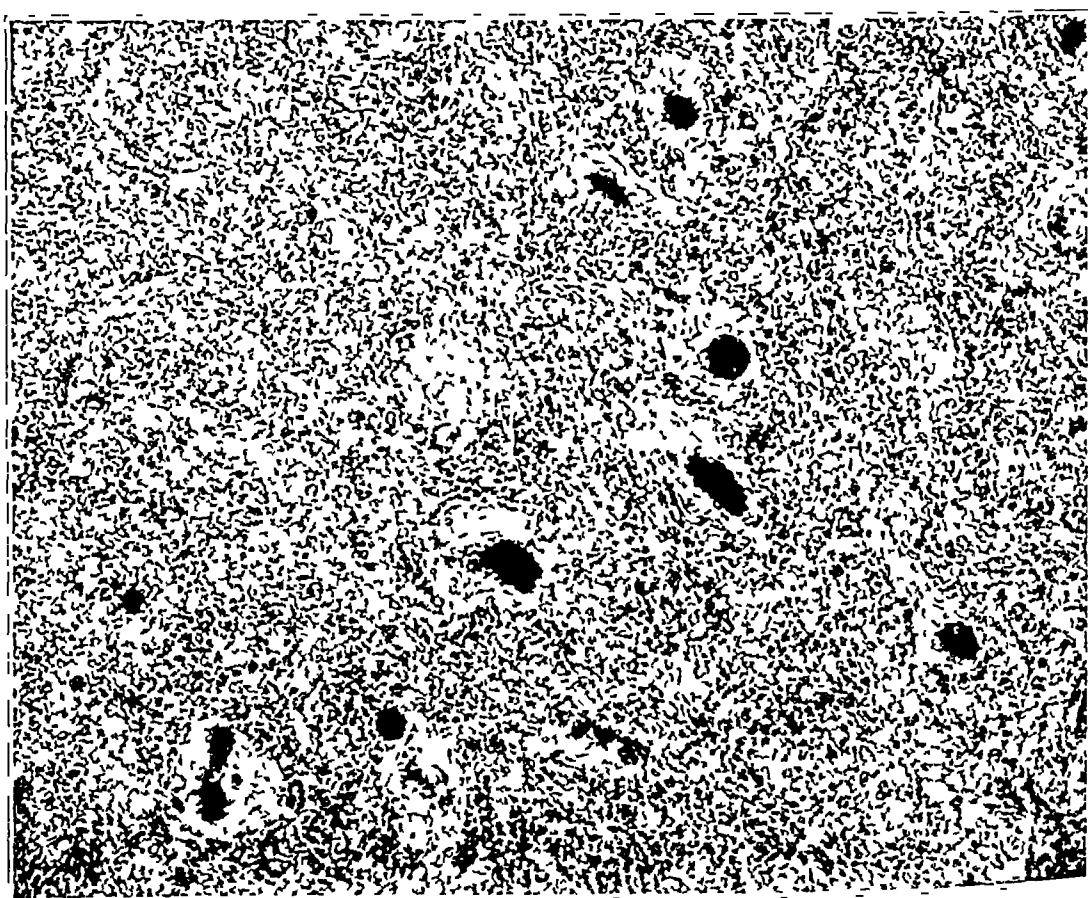


Fig 8 (case 2) —Photomicrograph (low power) showing fat within the ganglion cells of the hypoglossal nerve Ponceau stain for fat

The prostate and seminal vesicles, aorta, bone marrow, voluntary muscle and hypophysis were normal

*Brain*—The brain weighed 1,710 Gm. It was edematous and congested. Microscopically, severe widespread toxic degeneration of ganglion cells was noted throughout the cortex with a loss of ganglion cells in foci. The toxic degeneration of the cells also involved the cells in the hypothalamus, cerebellum and brain stem. Vessels with perivascular infiltration by lymphocytes were seen in the cortex and the basal ganglions, especially in the pallidum, pons and inferior cerebellar peduncle, a few were present in the white matter. Fat was found almost everywhere in even greater abundance than in case 1. It was found in the ependymal cells, vascular endothelium, astrocytes, microglia and ganglion cells everywhere except in the substantia nigra.

#### COMMENT AND RELATMENT

All the symptoms and signs which were observed in the two fatal cases can be explained by the pathologic changes. The widespread and extreme damage to the central nervous system in itself would seem sufficient to produce death, and that damage probably played a large part in the fatal issue. The most common neurologic manifestations in severe cases of poisoning from *Amanita phalloides* are those indicating a generalized cerebral involvement: confusion, delirium, coma and convulsions. Other symptoms and signs occurring less commonly include visual disturbances, pupillary disorders, ocular palsies, tremors, twitchings and changes in the tendon reflexes and plantar response. Clark, Marshall and Rowntree<sup>7</sup> concluded that the nervous symptoms may often be the result of uremia rather than of a "neurotoxin." In the case which they studied a marked retention of the blood urea and great diminution in the renal function were evident. The outcome was unusual, however, in that the patient survived for twenty-eight days. (In most fatal cases of poisoning due to *Amanita phalloides* death occurs at from the fifth to the eighth day.) Considerable secondary infection was also present (cystitis, parotitis and acute enteritis and colitis). Postmortem examination in their case revealed the usual changes in the liver and kidneys. No mention is made of examination of the central nervous system.

In both of our fatal cases, the urea nitrogen content of the blood was elevated at the time of the patient's admission to the hospital (33.3 and 42.4 mg. per hundred cubic centimeters, respectively). This appears to be explainable by the extreme dehydration observed in these patients, as in the second patient who survived long enough for the fluid balance to be restored the value fell to 16.2 mg. before death. From our studies it appears that the nervous symptoms and signs present in typical severe cases of poisoning due to *Amanita phalloides*

<sup>7</sup> Clark, M., Marshall, E. K., and Rowntree, L. G. Mushroom Poisoning, *J. A. M. A.* 64:1230 (April 10) 1915.



are the result of severe and widespread toxic damage to the cells of the central nervous system and not to uremia

Cases of poisoning caused by more than one variety of fungi are occasionally encountered. This is suggested by a number of the cases reported in the literature. Patients with that type of poisoning have a better prognosis than those who have ingested only *Amanita phalloides*, as the presence of other species initiates earlier gastro-intestinal reactions which aid in preventing absorption of the toxins of the "deadly" *Amanita*.

In the treatment of mushroom poisoning it should be remembered that extremely ill patients, even those with marked nervous symptoms, deep jaundice and evidence of renal damage, may recover completely (case 3). Care should be taken to keep the patients at complete rest until recovery is assured. Gautier<sup>8</sup> has reported a typical case of poisoning due to *Amanita phalloides* in which the patient was admitted to the hospital at the end of the second day and discharged improved on the seventh day. After a remission of nine days he was readmitted with prostration and nervous symptoms and later died in coma. Remissions of this length are not common, but several cases with remissions of two and three days are reported. In the two fatal cases in our series the patients seem to have suffered a severe aggravation of the condition by being moved a considerable distance by automobile on the third day of illness.

It seems probable that the less severe symptoms and shorter course in case 4 resulted from the fact that the patient had taken a saline purge before the appearance of symptoms, even though this was taken several hours after the ingestion of the mushrooms. In these four patients there was no relation between the rapidity of onset of symptoms and the outcome. The patient who became ill after seven hours, and whose illness was exceedingly severe, recovered, while the patient who was last affected (sixteen hours) succumbed. The mortality from poisoning due to *Amanita phalloides* is at least 50 per cent. The low mortality from poisoning due to *Amanita muscaria* is not the result of a low toxicity of the poison but is rather due to the fact that the early appearance of nausea, vomiting and diarrhea aid in preventing further absorption of the toxic substance.

In the treatment of the rapid type of mycetismus (*Amanita muscaria*), the early onset of vomiting and diarrhea is of value in removing the poisonous fungi from the gastro-intestinal tract. For this reason no attempt should be made to alleviate these symptoms. If the

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8 Gautier, P, and Saloz, C. Remission et survie prolongee dans un cas mortel d'empoisonnement par "l'amanite phalloide," *Rev med de la Suisse Rom* **37** 291 (May) 1917

stomach is not completely emptied, gastric lavage should be carried out with saline solution, or an emetic should be given. A saline purge may be left in the stomach after it has been irrigated or the cathartic may be administered by mouth to aid in emptying the lower portion of the gastro-intestinal tract. Atropine sulphate should be given at once hypodermically in all cases in which there is evidence of the action of muscarin (marked perspiration, salivation, lacrimation and pinpoint contraction of the pupils). In severe cases as much as  $\frac{1}{25}$  grain (0.0025 Gm.) may be given and the dose repeated after a few minutes. The intravenous route may be resorted to if the patient is moribund. In cases in which the patient shows symptoms of collapse, caffeine, strychnine and epinephrine should be given in full doses in order to tide him over the acute stage, after which recovery occurs rapidly.

The late onset of symptoms in the delayed type of mycetismus (*Amanita phalloides*) allows the fungi to be well down the gastro-intestinal tract before symptoms appear. Emetics and gastric lavage are of less value than in the other type of poisoning, but they should be employed at once to make certain that the stomach is empty. Thorough purging is especially important to empty the ileum and colon quickly. High enemas may be given. All the patients who are known to have eaten the same fungi but in whom symptoms have not appeared should undergo emptying of the gastro-intestinal tract at once by the same methods. Rest in bed is essential, and the patients should be kept quiet until recovery has definitely taken place. Relapse with a fatal issue is not uncommon in patients who have been ill several days and who are apparently improving. Opiates are usually indicated and should be given hypodermically for the relief of the severe abdominal pains and delirium and in order to induce sleep.

A liquid diet with high carbohydrate content should be given when possible because of the hepatic and renal damage. Forced administration of fluids should be resorted to in order to keep up the urinary output and aid in preventing dehydration and acidosis. Intravenous administration of dextrose in physiologic solution of sodium chloride, as first suggested by Blank,<sup>9</sup> appears to be of especial value for patients with marked and persisting gastro-intestinal symptoms. A 10 per cent dextrose solution should be used and from 500 to 1 000 cc. given every six to eight hours. Physiologic solution of sodium chloride given subcutaneously or tap water rectally may prove of value by increasing the intake of fluids. The presence of shock and circulatory collapse should be combated by the usual methods. External application of heat and the use of caffeine, strychnine and epinephrine (in full dosage) may be indicated.

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<sup>9</sup> Blank, G. Ueber Knollenblätterpilzvergiftung, München med. Wchnschr. 67 1032 (Sept. 3) 1920.

The use of an antitoxin serum has been advocated<sup>10</sup> in this type of poisoning and has been used in France and Germany. The serum is prepared by immunizing horses with increasing doses of toxin obtained from several varieties of *Amanita phalloides*. The results are difficult to evaluate, but from the reports the effects of the serum seem to be of some value. So far as we are able to determine, there is no similar antitoxin available in this country.

Recently a new type of treatment, based on experimental work with animals, has been suggested by Limousin and Petit<sup>11</sup>. It was found that cats succumbed within forty-eight hours after they had eaten a small amount of cooked *Amanita phalloides* (from 5 to 10 Gm). Rabbits were unaffected by a similar dose taken by mouth, but 0.5 cc of the juice of the mushroom proved rapidly fatal when injected subcutaneously. From this it was concluded that the toxin was neutralized or destroyed in the stomach of rabbits. The pathologic changes in the dead animals included gastro-enteritis, acute massive degeneration of the liver and acute glomerulo-epithelial nephritis. Cats receiving 10 Gm of *Amanita phalloides* with 100 Gm of fresh rabbit stomach survived for six days and at necropsy showed no hepatic damage; death was attributed to "nerve intoxication". Cats receiving 10 Gm of *Amanita phalloides* with 100 Gm of fresh rabbit stomach and 60 Gm of fresh rabbit brain survived. On the basis of these findings, Limousin and Petit treated patients with *Amanita phalloides* poisoning by giving fresh uncooked rabbit stomach and rabbit brain minced together. From three to five each of fresh rabbit brains and stomachs were given to the patients and in some cases the dose was repeated on successive days. The patients were thought to be definitely improved by the therapy despite the fact that some of them were not treated until the third day.

The conclusion of Limousin and Petit that recovery in their cases resulted from the treatment given should be investigated further. When one considers the high mortality rate from intoxication by *Amanita phalloides*, any type of therapy not in itself harmful is worthy of trial.

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10 Dujarric de la Riviere, R. Essai de serotherapie contre les empoisonnements par champignons veneneux, Bull Acad de med, Paris **94** 1000 (Nov 10) 1925, Etude d'une toxine vegetale la toxine phallinique, Ann Inst Pasteur **43** 961 (Aug) 1929. Schlossberger, H, and Menk, W. Zur frage der Serumbehandlung von Knollenblatterschwammvergiftungen, Klin Wchnschr **10** 1346 (July 18) 1931. Ford, W W. The Toxicological Constitution of *Amanita Phalloides*, J Exper Med **8** 437 (May) 1906.

11 Limousin, H, and Petit, G. Essai therapeutique au cours des intoxications par l'amanite phalloide. Bull Acad de med, Paris **107** 698 (May 24) 1932. Limousin, H. Essai de traitement des intoxications causees par les champignons veneneux, Presse med **40** 1685 (Nov 9) 1932.

# SUMMARY

1 Nearly all the severe cases of mushroom poisoning (mycetismus) seen in this country result from the ingestion of one of the varieties of the genus *Amanita*

2 For practical purposes these cases may be divided into "rapid" and "delayed" types

The rapid type of poisoning occurs within from one to three hours after ingestion of fungi of the *Amanita muscaria* group. This type of poisoning is characterized by excessive salivation, perspiration and lacrimation. Nausea, vomiting, severe abdominal pains and diarrhea occur. The pupils are contracted. Convulsions and coma are seen in the severe cases. The mortality is low, and the patients respond well to the proper treatment.

The delayed type of mycetismus results from the ingestion of mushrooms belonging to the *Amanita phalloides* group. The onset is delayed until from six to fifteen hours or more after ingestion of the fungi. Abdominal pains are severe, and nausea and vomiting may be extreme. Diarrhea is nearly always present. The patients are prostrated from the onset. Jaundice nearly always occurs, and renal damage is frequent. Symptoms resulting from damage to the central nervous system are usually present. The mortality in this type of poisoning is at least 50 per cent.

3 Four cases of poisoning by *Amanita phalloides* are reported, and complete pathologic studies on two fatal cases are given. Extreme degenerative changes were found in the parenchymal cells of the liver and to a lesser extent in the tubular epithelium of the kidneys. In both patients there was severe widespread damage to the central nervous system. The brains were congested and edematous and on microscopic section degenerative changes were observed in the cells of the cortex, hypothalamus, cerebellum and brain stem. Fat was found almost everywhere throughout the brain, and there were scattered areas of perivascular infiltration with lymphocytes.

4 The treatment of mushroom poisoning is discussed.

# HABITUAL HYPERTHERMIA

## A CLINICAL STUDY OF FOUR CASES WITH LONG CONTINUED LOW GRADE FEVER

HOBART A. REIMANN, M.D.

MINNEAPOLIS

Patients with continuous low grade fever lasting months or years who are otherwise physically well frequently present perplexing problems to the clinician. Even after prolonged fruitless investigation one hesitates in most cases of this nature to dismiss the matter lightly lest some unrecognized or occult lesion be present. Yet few physicians have the opportunity and few patients the time and money necessary for investigation and observation over long periods. The patient with such a condition often becomes dissatisfied with the negative results of repeated examinations by his own physician and commences a tour to a long series of physicians, as illustrated in the following reports of cases. As often happens, each physician approaches the case from a different point of view and arrives at a different conclusion, until the patient is alarmed by the array of suggested diagnostic possibilities and, if not already neurotic, may become so. Besides this the patient is often successively deprived of teeth, tonsils and thyroid gland, is subjected to other needless procedures and operations, is regarded as a potential invalid and obliged to lead an unnecessarily restricted life or is rendered impecunious by the expenses involved.

There has been considerable discussion of this problem in recent years, largely in European journals.<sup>1</sup> Persons with low grade fever lasting for years without evident cause have been regarded as having "constitutional subfebrility," an "unstable nervous system," "psychogenic fever," "neurosis" and so on. The term "habitual hyperthermia," which implies the constant existence of the temperature at levels higher than those accepted as normal, was introduced by Moro in 1917. The term appears to be satisfactory until further knowledge renders it obsolete. Other terms suggesting a psychic or neurogenic origin of the fever are less satisfactory since in certain cases the condition does not appear to be due to this cause. Frequently however, as illustrated in three of the four cases reported here, patients regarded as neurotic have a

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1 Reimann, H. A. Habitual Hyperthermia, J. A. M. A. 99:1860 (Nov. 26) 1932. Additional references to the literature are given in this article.

temperature slightly higher than normal. The question remains whether the elevated temperature is due to the neurosis or the neurosis to the hyperthermia or whether both are part of a certain constitutional state. In some cases abnormalities of temperature appear to be related to evident or obscure disturbances of the endocrine system. The fever of hyperthyroidism is well known. It is also evident from experimental studies and clinical observations that destruction of the suprarenal glands is accompanied by a fall of temperature and that the normal level may be restored by the administration of extracts of the suprarenal cortex. Changes in temperature in some women are clearly related to the menstrual period<sup>1</sup> or to ovulation<sup>2</sup>. There is no doubt, therefore, that many factors aside from those which are well known may influence the regulation of body temperature.

In the case of patients who exhibit hyperthermia over long periods of time, even if otherwise apparently healthy, it is always essential to search for underlying causes, whatever their nature. Among these causes may be mentioned a number of infections, chiefly tuberculosis, subacute bacterial endocarditis, undulant fever, rheumatic fever, malaria and possibly focal infection, which may be present for long periods with minimal clinical symptoms and signs. A number of other conditions must also be considered, such as renal calculus, neoplasm, Hodgkin's disease, anemia, disturbance of the endocrine glands, especially hyperthyroidism, diabetes, pregnancy, menstruation, dehydration, chronic poisoning, heart failure, postencephalitic rests, organic disease of the brain and tumor of the brain or cord. Many cases of prolonged fever observed carefully over a sufficient period eventually prove to be due to one of the conditions mentioned. Yet a number of patients continue to have low grade "fever" for twenty years or more without evidence of organic dysfunction and without symptoms, signs or complaints. This observation raises the question as to what constitutes a "normal" temperature. Reports from time to time indicate that certain variations exist for different persons and for animals. This variation seems reasonable, for if the pulse rate varies from 50 to 90 beats per minute and the blood pressure from 90 to 140 mm of mercury in different normal persons,<sup>3</sup> one would expect the temperature of normal persons to vary over a considerable range. The usually accepted average normal oral temperature is 37° C (98.6° F), although Whiting<sup>4</sup> found the average oral temperature in six hundred and twenty healthy convicts

2 van de Velde T. H. cited by Harvey and Crockett<sup>9</sup>

3 Addis T. Blood Pressure and Pulse Rate Levels, *Arch. Int. Med.* **29** 539 (April) 1922

4 Whiting, M. H. On the Association of Temperature, Pulse and Respiration with Physique and Intelligence in Criminals. A Study in Criminal Anthropometry, *Biometrika* **11** 1, 1915

to be 36.8 C (98.25 F), and Lyon and Wallace<sup>5</sup> in a large series of nonambulatory patients found 36.2 C (97.2 F) to be the average temperature at 7 a. m. and 36.35 C (97.45 F) at 7 p. m. Although the mean temperatures reported by these authors are dissimilar, the standard deviations calculated by Dr. Frances Vanzant from the data are practically identical, being 0.49, 0.455 and 0.46, respectively. Because of the remarkable uniformity of the values, it seems justifiable to use the weighted average value, 0.47, to calculate the theoretical distribution of temperature readings in normal persons, using the accepted mean of 37 C (98.6 F). The accompanying table prepared by Dr. Vanzant shows the percentage of probability of occurrence for each 0.2 F. in a normal population. The data indicate what a small proportion of persons have a temperature of exactly the accepted normal

*The Percentage Probability of Occurrence for Each 0.2 F. of Oral Temperature in a Normal Ambulatory Population*

Temperature, F	Percentage Probability	Temperature, F	Percentage Probability
Below 97.0	0.01	98.6 to 98.79	16.64
97.0 to 97.19	0.13	98.8 to 98.88	13.59
97.2 to 97.39	0.40	99.0 to 99.19	9.74
97.4 to 97.59	1.12	99.2 to 99.39	5.57
97.6 to 97.79	2.80	99.4 to 99.59	2.80
97.8 to 97.99	5.57	99.6 to 99.79	1.12
98.0 to 98.19	9.74	99.8 to 99.99	0.40
98.2 to 98.39	13.57	100.0 to 100.19	0.13
98.4 to 98.59	16.64	100.2 to 100.39	0.01

level and how frequently a temperature which is ordinarily regarded as evidence of fever is encountered in normal persons.<sup>6</sup> High normal temperature will no doubt be discovered more and more frequently with the increasing popularity of examinations for social health insurance.

The fact that four persons with temperatures at fever levels in whom no underlying organic cause could be found were encountered in a rather small medical service at the University Hospital further indicates that the condition occurs sufficiently often to be considered important. Other recent studies<sup>7</sup> substantiate this observation. Since the publication of

5 Lyon, D. M., and Wallace, H. L. The Mean Temperature in Non-Febrile Hospital Patients, *Brit. M. J.* **1**: 980 (May 28) 1932.

6 Wunderlich, C. A. *Medical Thermometry*, London, New Sydenham Society, 1871, vol. 49, p. 100. Pembrey, M. S., in Schafer, E. A. *Textbook of Physiology*, Edinburgh: Y. J. Pentland, 1898, vol. 1. Ceredi, A., and Nanni, G. Great Frequency of Subfebrile Temperatures, *Boll. d. sc. med., Bologna* **104**: 27 (Jan.-Feb.) 1932.

7 Gelmann, I. G. Zur Frage Aetiopathogenese protrahierter subfebriler Zustände, *Deutsches Arch. f. klin. Med.* **176**: 290 (March 15), 581 (Aug. 22) 1934. Kintner, A. R., and Rowntree, L. G. Long Continued, Low Grade, Idiopathic Fever, *J. A. M. A.* **102**: 889 (March 24) 1934. Csepai, K. Subfebrile Temperature as Mass Phenomenon, *Orvosi hetil.* **77**: 577 (July 8) 1933.

the report of a case in a patient first seen in 1931,<sup>1</sup> three others have been observed. All four patients were thoroughly studied during several periods of observation in the hospital without the cause for the elevated level of the temperature being determined. A number of tests, including those proposed by Holló and Holló-Weil,<sup>8</sup> were applied in an attempt to establish a diagnosis of "habitual hyperthermia." Holló and Holló-Weil claimed that fever of infectious origin can be differentiated from the type of fever in question by pharmacologic methods. Fever due to infection is reduced by antipyretic drugs but not by opiates. Fever not due to infection is not influenced by antipyretics but is suppressed by opiates.

#### REPORT OF CASES

**CASE 1—History**—This case was reported in detail previously.<sup>1</sup> Miss B. E., a student aged 26, was first observed in June 1931. "Fever" had been noted since the age of 5 years after an attack of measles. She had been treated for eighteen years as a potential invalid, suspected of having tuberculosis, because of the fever, although she felt and looked well. Her temperature, which was carefully registered from 1928 to 1930, showed a remarkably regular wavelike curve in distinct relation to the menstrual periods. Her oral temperature taken in the morning

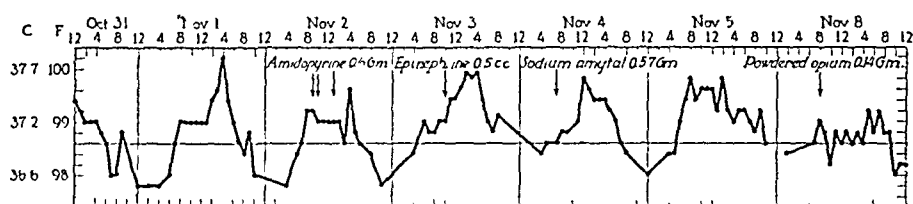


Chart 1—The temperature curve in case 1, showing the lack of response to amidopyrine and epinephrine, the apparent depressing effect of sodium amytal and the effect of opium in lowering the temperature.

before rising remained at 36.7 C (98 F) during the first half of the menstrual cycle. In the middle of the period it rose abruptly to 37 C (98.6 F) where it remained until the day preceding the menstrual flow when it abruptly dropped to the lower level. The behavior was so regular as to describe a curve resembling a Greek fret when plotted. The changes in temperature bore the same relationship to the menstrual period as the changes described in the case of the patient observed by Harvey and Crockett.<sup>9</sup> The temperature in the afternoon was usually above the normal level and was elevated further by physical or emotional strain. The highest peaks (37.8 C, or 100 F) were reached in the second half of the menstrual period. The mean afternoon temperature for four hundred and twenty days was 37.2 C (98.9 F), with a standard deviation of 0.23. The mean 8 a. m. temperature was 36.8 C (98.2 F), and the standard deviation, 0.3.

After thorough investigation the patient was informed that no underlying pathologic condition could be determined. She was advised to cease recording her

<sup>8</sup> Holló, J., and Holló-Weil, E. Experimentelle Analyse der subfebrilen Temperaturen und ihre Ergebnisse, Berl. klin. Wchnschr. 55:640, 1918.

<sup>9</sup> Harvey, O. L., and Crockett, H. E. Individual Differences in Temperature Changes of Women During the Course of the Menstrual Cycle, Human Biol. 4:453, 1932.



temperature and to lead a normal existence. Her outlook on life has been greatly improved by the assurance that she is normal.

She was observed at intervals during the next three years, during which time no changes occurred. Except for an occasional "cold," she was perfectly well. The patient reentered the hospital for further tests in October 1933. All of the results of the physical examination and laboratory observations were negative. The temperature when measured frequently registered above the normal level.

*Experimental Study*—During two days of observation the temperature was measured every two hours. The lowest levels occurred between 12 p. m. and 4 a. m. and the highest at 4 p. m., representing a range of 1.2 C (2.2 F). The patient was then given 0.6 Gm. of amidopyrine at 9 a. m., 10 a. m. and 1 p. m., according to the suggestion of Hollo. There was practically no antipyretic effect. The next day she was given subcutaneously 0.5 cc. of a 1:1,000 solution of epinephrine chloride without the striking effect obtained by Cawadias<sup>10</sup> in his patient. On the fifth day the administration of 0.57 Gm. of sodium iso-amylethyl barbiturate (sodium amytal) by mouth produced drowsiness and sleep lasting about two hours but had little effect on the temperature. On November 8, 0.14 Gm. of powdered opium given by mouth caused restlessness followed by a sense of profound relaxation for several hours but no sleep. The pulse rate dropped from 80 to 68, and the temperature was distinctly lowered for six hours. The temperature curve is illustrated in figure 1.

*Comment*—This patient's condition is an example of "habitual hyperthermia." She was not neurotic and appeared to be normal in every way except in respect to the level of temperature. The temperature had apparently been higher than the usual normal level for at least twenty-one years. The level was not influenced by antipyretics but was depressed by opium, in accordance with the behavior of "normal" temperature.

*CASE 2—History*—Miss R. L., a nurse aged 38, dated the onset of her illness from January 1931, when she first noted weakness and dizziness. Soon after, tachycardia (heart rate of 140) occurred, but at times she became alarmed because the rate dropped to 60. Periods of "dyspnea" were followed by hyperpnea. She could not lie on her right side because of a choking sensation. For seven months prior to the stated onset of her illness she noted that her temperature frequently registered 37.6 C (99.6 F) in the afternoon, at which time she felt weak and tired. On closer questioning she stated that in 1928 and at intervals thereafter her temperature when measured was 37.6 C (99.6 F).

In February 1931 she visited a physician who suspected toxic goiter and sent her to a hospital for six weeks. Her basal metabolic rate was found to be +6, +15 and +12. An electrocardiogram showed "myocardial weakness." The temperature frequently rose to 37.6 C (99.6 F). After a prolonged course of therapy with compound solution of iodine, U. S. P., solution of potassium arsenite, U. S. P., digitalis and salicylates she left the hospital unimproved. Another physician then advised her to remain in bed until the fever disappeared. She remained in bed for three months during which time the temperature reached the fever level daily. She returned to work for about a month, noting occasional tachy-

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<sup>10</sup> Cawadias, A. La fièvre continue d'origine sympathétique, *Ann. de med.* 7:450, 1920.

cardia and bradycardia. She would awaken at night with a sensation of smothering. At times she thought she detected missed heart beats. A third physician advised rest in bed on account of "endocarditis." She remained in bed for ten months. A fourth physician diagnosed auricular flutter and again administered digitalis. In March 1932 a murmur believed to be due to mitral stenosis was noted. She then began to complain of prickling, tingling, blueness and coldness of her feet when she attempted to stand. Exertion or excitement increased her heart rate to 140 and caused tachypnea. Vertigo and *muscae volitantes* were noted.

The patient entered the University Hospital in August 1932 complaining of a rapid, pounding heart beat, a sense of fulness "as if the heart valves were too small," a sense of choking, swelling of the ankles and hands, blueness of the legs and arms when held dependent and general nervousness. She was most worried by the possibility of tuberculosis. She had spent most of the fifteen months prior to admission in bed and had gained 27 pounds (12.2 Kg). Her history was unimportant. Except for repeated severe attacks of tonsillitis in childhood her health had been good. The menstrual cycles were normal and regular. Her tonsils and hemorrhoids were removed in 1921. Several teeth were extracted in 1930. Roentgen examination of the chest in 1931 gave negative results and a tuberculin test was positive. Her mother had died of tuberculosis in 1909 at the age of 49. One brother died of tuberculosis in 1915. One sister had undergone thyroidectomy for complaints similar to those of the patient.

Physical examination revealed a pale, pudgy, well developed, flabbily obese woman weighing 171 pounds (77.6 Kg). The swelling of the hands and ankles noted by the patient appeared to be due to adiposity. The corneal and pharyngeal reflexes were sluggish. The heart and lungs were normal. The heart rate varied from 60 to 120, after exercise it was 144 and while the patient was asleep, 60. The blood pressure varied from 126 to 144 mm of mercury systolic and from 72 to 76 mm diastolic, during sleep it was 100 systolic and 70 diastolic. The respiratory rate was normal at all times. When the legs were held over the edge of the bed they became cyanotic and cold in a few minutes. The patient said they also became numb.

Laboratory tests and roentgenographic studies of the heart and lungs gave negative results. Electrocardiograms on three occasions were normal. The sedimentation time of the blood was normal. The basal metabolic rate was plus 1 and minus 9 per cent. Intradermal injection of old tuberculin (0.1 mg) on two occasions produced erythema and an induration of  $1\frac{1}{2}$  inches (3.8 cm) diameter in forty-eight hours without focal or general reaction.

*Temperature*.—During most of the three month period of observation the oral temperature was measured at four hour intervals during the day. It fluctuated between 37°C (98.6°F) and 37.4°C (99.3°F), occasionally not touching the normal level for several days. The mean temperature was 37.1°C (98.7°F) at 8 a. m. and 37.3°C (99.1°F) at 4 p. m., with standard deviations of 0.54 and 0.38, respectively. There was a slight tendency to somewhat higher levels one week preceding the menstrual period. Registrations made at shorter intervals during the day and night showed a greater range of fluctuation. The level was usually highest in the late morning, though seldom over 37.7°C (99.8°F). At midnight it occasionally registered 36°C (96.8°F). The highest temperature observed was 38°C (100.4°F), which indicates a range of 2°C (3.6°F).

The patient talked readily and at length about her symptoms and appeared to be nervous and apprehensive. She was convinced by previous physicians that she had cardiac disturbance and was now worried about tuberculosis. She was often irritable and complained about the nursing service and other matters. She was

greatly displeased at the inability of the physicians to detect any organic abnormalities to account for her symptoms and left the hospital suddenly in a display of violent temper

*Experimental Study*—The patient was given 4 Gm of sodium salicylate on one day and 12 Gm of amidopyrine in divided doses on another day without evidence of antipyresis. A dose of 0.36 Gm of phenobarbital followed by 0.015 Gm of morphine produced drowsiness and dozing which lasted several hours, during which time the temperature was subnormal at a time of the day when it was almost invariably at a fever level (fig 2). Curiously, however, anesthesia lasting two hours after the rectal instillation of 38 cc of tribromethanol (avertin) failed to lower the temperature. Administration of 0.5 cc of a 1:1,000 solution of epinephrine chloride failed to produce a striking change in the temperature and pulse rate. No effect was noted after the daily administration of 0.18 Gm of thyroid for ten days. On November 9, the final day of observation, when the patient exhibited sudden violent anger the temperature shortly after the outburst reached 38 C (100.4 F), the highest peak observed during three months (fig 2).

*Course*—After leaving the hospital the patient went directly to another physician who gave her compound solution of iodine, U S P, and subsequently removed the thyroid gland, which was slightly enlarged. Her temperature was measured

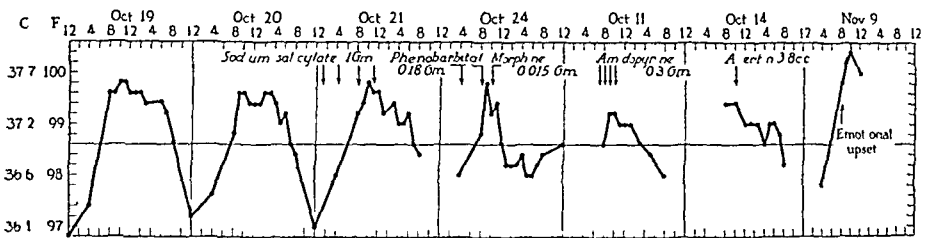


Chart 2—The temperature curve in case 2, showing the relative effects of certain antipyretic and sedative drugs and the effect of psychic stimulation on the temperature level

before and for a short time after thyroidectomy and was found to be elevated as usual. When the patient was induced to visit the hospital again for observation about a year later (November 1933), she stated that most of her symptoms had disappeared. She had maintained a rigid diet and had lost 14 pounds (6.4 Kg) or about one half of the excess weight which had previously been gained by prolonged rest in bed. She then undertook work as a housemaid and lost another 14 pounds (6.4 Kg), which restored her weight to normal. She refused to submit to examination other than the measurement of the temperature and pulse. However, her lips were cyanotic, the heart rate was 112, and the temperature, 37.3 C (99 F).

*Comment*—This patient was definitely neurotic. She was anxious to establish her symptoms, real and imaginary, on an organic basis, and until the thyroid gland was removed she obtained no benefit. I do not believe that she suffered from hyperthyroidism or from any of the numerous other diseases suggested by the physicians consulted, but the psychic effect of operation and the later resumption of work appeared to relieve her of the multifarious symptoms. The fact that the temperature and pulse rate were still elevated one year after thyroid-

ectomy indicates no relationship in this case to thyroid dysfunction. She was regarded as a neurotic person with cardiac and vasomotor instability and habitual hyperthermia. Her temperature was not influenced by antipyretics, was depressed by morphine and was increased by emotional excitement.

CASE 3—*History*—Miss K. U., aged 35, was born in Poland, suffered much during the World War and came to the United States in 1926. She was very homesick, oriented herself with great difficulty and lived unhappily with relatives. She obtained work as a dish-washer. In March 1927 she had a severe cold, sore throat and pains in the chest which confined her to bed for a month. She recovered from the acute attack, but her physician noted that the temperature persisted at about 37.7 C (99.8 F) and enforced rest in bed for five months. After this the patient never felt equal to resuming work because of weakness. Roentgenograms of the chest showed nothing abnormal. The tonsils were removed because of the fever. After about a year of observation she was sent to a sanatorium for the treatment of tuberculosis for six months. Slight fever was noted almost daily, but she was discharged as nontuberculous. In October 1930 her physician first noted nystagmus, although the patient and her relatives had noted it since the onset of her illness in 1927. Because of indefinite abdominal distress she was examined for peptic ulcer in 1931. A Mantoux test performed in 1932 was said to have been positive.

The patient first came to the University Hospital in April 1933. She complained of indefinite pains in the back of the neck, chest, abdomen and arms and of insomnia, constipation, belching, occasional headache and dizziness but especially of weakness. The symptoms were usually worse in the winter. Her menstrual history was unimportant.

Physical examination revealed a reticent, sensitive woman apparently in good health. She was conversant and cooperative but cried easily during questioning and stated that she was almost without hope of getting well and returning to work. She usually sat or lay quietly, doing nothing and exhibiting little interest in her surroundings. She moved and talked slowly. Her weight was 119 pounds (54 Kg). Only two abnormalities were discovered—nystagmus and hyperthermia. There was an almost constant nystagmus of the third degree. On looking straight forward, nystagmus was vertical with the quick component down, on looking to the left, it was either vertical or horizontal with the quick component to the left. On looking to the right the same type of nystagmus occurred except that the quick component was to the right. All other ophthalmoscopic, otolaryngoscopic and neurologic tests performed by various consultants during several periods of hospitalization revealed no different or further results. The results of the chair and of the caloric test and the hearing and the eyegrounds were normal, and the tests of the visual fields gave normal results.

The thyroid gland was palpable and slightly enlarged, and there was slight acropachy of all of the fingers. A systolic murmur was audible. The blood pressure was 125 mm of mercury systolic and 80 mm diastolic. Roentgenograms of the sinuses, the chest, the spine and the mediastinum showed no abnormalities. The injection of 0.01 mg of old tuberculin intradermally produced a raised indurated area 2 cm in diameter in twenty-four hours without focal or general reaction. The Brucella skin test gave a negative reaction. The laboratory data were all normal including the results of the morphologic studies of the blood, and the examination of the spinal fluid, the sedimentation time, the electrocardiogram, the

Wassermann reaction and the agglutination tests for undulant fever and typhoid. The basal metabolic rate was  $-4$  and  $-6$  per cent on two occasions.

The patient was discharged in July 1933 after an observation of three months and was readmitted in September 1933 for six weeks' and in April 1934 for three weeks' observation. During these intervals one physician administered vaccine intravenously for "arthritis" and another tested her for hypersensitivity to a large number of proteins without positive results. Laboratory tests and clinical observation revealed no new information during the subsequent periods of observation. The complaints, the temperature, the weight and the reaction to tuberculin remained as during the first observation.

**Temperature**—During the entire period of observation of about five months there were only three days on which the temperature failed to rise above  $37^{\circ}\text{C}$  ( $98.6^{\circ}\text{F}$ ). When readings were made at two hour intervals during the day the temperature invariably exceeded this level. The lowest reading recorded at these intervals was  $35.7^{\circ}\text{C}$  ( $96.2^{\circ}\text{F}$ ), a maximum range of  $1.8^{\circ}\text{C}$  ( $3.4^{\circ}\text{F}$ ). The lowest temperatures occurred between 12 p m and 2 a m (fig 3). The average temperature at 8 a m was  $36.9^{\circ}\text{C}$  ( $98.4^{\circ}\text{F}$ ), with a standard deviation of 0.41, and at 4 p m,  $37.2^{\circ}\text{C}$  ( $98.9^{\circ}\text{F}$ ), with a standard deviation of 0.27. As in cases 1 and 2, the temperature tended to reach its highest levels in the second half of the menstrual cycle.

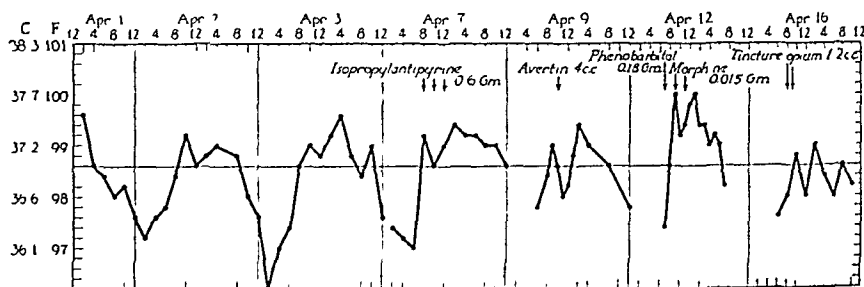


Chart 3—The temperature curve in case 3, showing the wide daily fluctuations and the effects of certain antipyretic and sedative drugs on the temperature level.

**Experimental Study**—Amidopyrine, 1.8 Gm, given in divided doses on several occasions, and a derivative of isopropylantipyrine,<sup>11</sup> 1.8 Gm, had no antipyretic effect. Hypodermic injection of 30 mg of morphine sulphate failed to produce narcosis but appeared to cause excitement, restlessness and nausea and elevation of the temperature to a higher level than usual. A small dose of 12 cc of tincture of opium failed to influence the level, but 26 cc caused several hours of drowsiness and intermittent light sleep, during which time the temperature appeared to be lowered (fig 3). Anesthesia lasting for ninety minutes induced by the rectal instillation of 4 cc of avertin was also accompanied by a depression of the temperature and by a decrease of 30 mm of mercury in the systolic blood pressure. Ingestion of 0.45 Gm of sodium amytal by mouth produced drowsiness and a short period of sleep without depressing the temperature. Antispasmodics of smooth muscle, such as benzyl succinate, 4 Gm, and mono-bromosalicyl alcohol likewise had no influence on the usual temperature level.

Sudden strenuous exercises like climbing and descending five flights of stairs for fifteen minutes and the hypodermic injection of 0.5 cc of epinephrine

11 This drug was supplied by Hoffmann-LaRoche, Inc.

chloride failed to cause a significant rise in temperature. The intravenous injection of 0.2 cc of typhoid vaccine was followed in two hours by a chill and a rise in temperature to 38.3 C (101 F).

*Comment*—It appears that the type of neurosis affecting this patient differs from that observed in case 2. The patient in case 3 appeared to be of the depressed, indolent or morose type in whom one would expect to find a temperature lower than the normal. No definite explanation can be advanced to account for the permanent nystagmus. Several consultants have inclined to my suggestion that both the nystagmus and the elevation in temperature were due to the residual effects of encephalitis which may have occurred during her illness in 1927. But the records of this illness do not bear this out. Multiple sclerosis, tumor of the brain or cord and tuberculoma were considered but not substantiated by facts. The history of emotional unrest, immigration and its attendant difficulties and unpleasant home life was conducive to the development of a neurosis which in my opinion was the underlying cause of the complaints. The temperature was not influenced by antipyretics but was depressed by certain narcotics, thus indicating its noninfectious origin.

*CASE 4—History*—Miss E. R., aged 47, stated that she had felt tired and weak all her life and had suffered continually from cold and aching feet and hands. In 1920 she noted a slight cough, pain in the chest and left arm, generalized aching pains and increasing weakness. She visited a physician who diagnosed the condition as neuritis and sent her to a hospital for a month's observation. No abnormal changes were discovered except that the temperature, which was measured twice a day, was frequently as high as 37.6 C (99.6 F). She was discharged with a diagnosis of chronic bronchitis. She thought that she did not improve, and another physician in 1921 removed her tonsils and all of her teeth because of the fever and told her that she had inflammation of the heart and possibly tuberculosis. The patient was then sent to a sanatorium for the treatment of tuberculosis for fourteen months. During this time the oral temperature in the afternoon was almost constantly higher than 37 C (98.6 F), but it never exceeded 37.8 C (100 F). She was unaware of fever. The pulse rate varied from 60 to 90. Her weight increased from 123 to 146 pounds (55.8 to 66.2 Kg). She was discharged as nontuberculous.

For a number of years she maintained a fairly normal amount of activity but always felt tired, had aching pains and was weak. In 1929 because of pains in the legs she visited a clinic, where a diagnosis of thrombo-angitis obliterans was made. After various forms of treatment she was discharged "completely relieved." In 1931 she visited another clinic complaining of pains in the muscles and joints, extreme weakness, itching, numbness and tingling of the feet and somnambulism. Because of the presence of achlorhydria, a hemoglobin content of 60 per cent and an erythrocytic count of 3,500,000, a diagnosis of pernicious anemia was made, and treatment with raw liver was instituted. The anemia was corrected, but eosinophilia (percentage, 58) developed, probably as a result of the treatment. Eosinophilia persisted for several months. In 1932 she was admitted to another hospital for the investigation of the cause of the eosinophilia. At this time the complaints were weakness, sleepiness, numbness, an itching skin, aching pains,

dizzy spells, perspiration, ravenous appetite, dyspnea, palpitation and purring inside the chest. Nothing could be found to account for these symptoms. The physical examination and the roentgenographic studies of the chest, gastro-intestinal tract, spine and ribs gave negative results. Laboratory studies revealed nothing significant except the eosinophilia, which was diminishing. The basal metabolic rate on two occasions was  $+9$  and  $-13$ . During this visit and six subsequent visits to the hospital the patient was given many injections of typhoid vaccine without any relief of symptoms. A temperature varying from  $37.3^{\circ}\text{C}$  ( $99.2^{\circ}\text{F}$ ) to  $37.9^{\circ}\text{C}$  ( $100.2^{\circ}\text{F}$ ) was noted continually.

By this time the patient's financial resources were exhausted, and she was referred to the University Hospital on April 7, 1934, for further study. Nothing need be added to the voluminous record except that the family history was irrelevant. Menstruation had always been irregular and had ceased five years before. The chief complaints were abdominal pains and distention. She was rather pale but cheerful, intelligent, cooperative and anxious to discuss her case. No abnormal physical signs were found. The weight was 136 pounds (61.7 Kg). Both dorsalis pedis arteries were pulsating, and a determination of the vasomotor index gave a normal value. The roentgenographic and laboratory studies gave normal results, including the sedimentation time and the morphologic characteristics and number

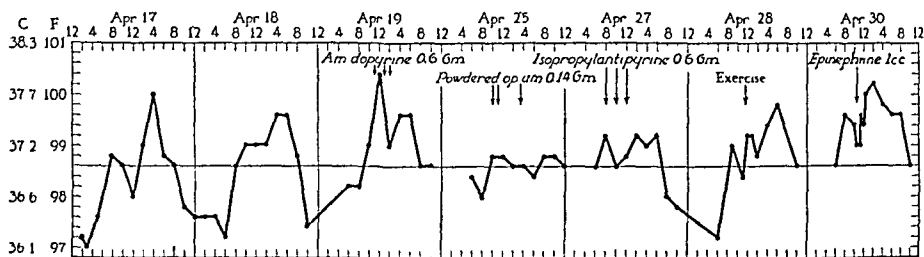


Chart 4—The temperature curve in case 4, showing the effect of various drugs on the temperature level

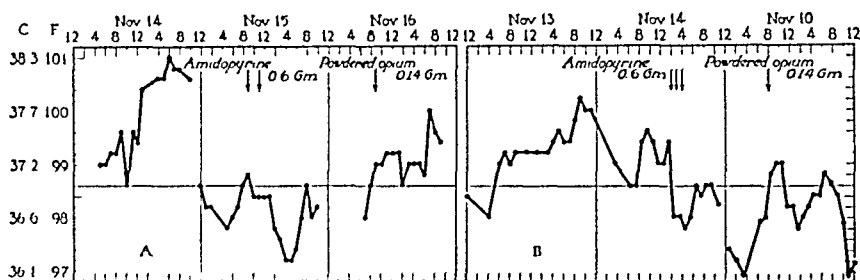
of the blood cells. The basal metabolic rate was  $-15$ , and the temperature measured  $37.2^{\circ}\text{C}$  ( $98.9^{\circ}\text{F}$ ). Achylia gastrica was present. The weight was 143 pounds (64.9 Kg). The Mantoux test produced an area of erythema 2 cm in diameter with the injection of 0.1 mg of old tuberculin.

*Temperature*—The oral temperature, measured at two hour intervals, was subnormal during the night, ranging from  $36.1^{\circ}\text{C}$  ( $97^{\circ}\text{F}$ ) to  $36.3^{\circ}\text{C}$  ( $97.4^{\circ}\text{F}$ ), and usually reached its highest point in the afternoon, varying from  $37.6^{\circ}\text{C}$  ( $99.6^{\circ}\text{F}$ ) to  $37.8^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). The highest level observed was  $38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). The average morning temperature was  $36.9^{\circ}\text{C}$  ( $98.4^{\circ}\text{F}$ ), with a standard deviation of 0.55, and the average afternoon temperature,  $37.4^{\circ}\text{C}$  ( $99.3^{\circ}\text{F}$ ), with a standard deviation of 0.28. The curve of the pulse rate paralleled that of the temperature in its rise and fall and ranged from 66 to 90 beats per minute.

*Experimental Study*—Amidopyrine and a derivative of isopropylantipyrene failed to lower the temperature, while powdered opium, which caused drowsiness and light sleep for an hour or two, apparently lowered the level (fig 4). Benzyl succinate, 4 Gm, failed to influence the curve. Rapid climbing of stairs for ten minutes had no appreciable effect on the temperature, nor did the subcutaneous injection of 1 cc of a 1:1,000 solution of epinephrine chloride (fig 4).

*Comment*—It is possible that neurosis was aggravated in this patient by medical oversolicitude. The array of suggested diagnoses and the amount of treatment given no doubt have a definite mental effect on a certain type of person. The temperature, maintained for fourteen years at a fever level, which caused concern to physicians but not to herself, probably has no significance. The condition failed to respond to antipyretic drugs and was depressed by opiates, as would be expected in a normal person.

**CASE 5**—This case constituted a diagnostic problem and illustrates the difficulties encountered in cases of this type in determining the cause or nature of the fever. Miss R. R., a nurse aged 22, had acute rheumatic fever at the age of 4 years. In 1931 sudden pain developed in the epigastrium which troubled her more or less after that. All results of studies at this time were negative except that a temperature of from 37.2 C (99 F) to 37.8 C (100 F) was constantly present during the day. The appendix was removed, but the symptoms persisted. For the next two years she spent part of her time in bed because of tiredness and weakness. On one occasion pains in the joints occasioned a diagnosis of recurrent



**Chart 5**—A shows the antipyretic effect of amidopyrine and the slight depressant effect of opium on the temperature in a case of undulant fever. B shows that in case 5, in which the elevated temperature was believed to be of infectious origin, amidopyrine and opium both caused a fall of temperature.

acute rheumatic fever. In 1933 the patient returned to the hospital where she has been confined in bed to the time of writing this report. The chief complaints are occasional pain in the epigastrium and in the right upper quadrant, vomiting, weakness and nervousness. The nervousness and irritability are markedly increased during the menstrual period. Rheumatic infection, tuberculosis, undulant fever, subacute bacterial endocarditis and Hodgkin's disease were considered as diagnostic possibilities.

Physical examination revealed a well nourished but pale, nervous and apprehensive person. No abnormalities except a short, high-pitched diastolic murmur along the left sternal edge were discovered in the chest. There was tenderness deep in the right upper flank. Cystoscopy and intravenous and retrograde pyelograms were negative. All of the laboratory tests including blood cultures, tests of the sedimentation time, numerical and morphologic studies of the blood cells and roentgenographic studies gave negative results. Agglutinins for Brucella were of insignificant titer. The number of leukocytes averaged from 5,000 to 6,000. The Mantoux test was slightly positive.

The temperature was with few exceptions elevated in the daytime during the eight month period of observation. In contrast to the temperature levels of the



four patients just described, it tended to be more irregular. For several weeks it seldom exceeded 37.8 C (100 F) except for occasional peaks of 38.3 C (101 F). At other times it reached 39.5 C (103 F) or 39.7 C (103.5 F) for several days and was occasionally accompanied by a chill. The patient felt ill during these periods and was fully conscious of the fever. The temperature on one occasion appeared to be uninfluenced by the employment of 1.2 Gm of amidopyrine, on another it dropped abruptly after the administration of 1.8 Gm from 37.4 C (99.4 F) to 36.7 C (98 F) and remained low during the day (chart 5). The antipyretic effect was typical of that produced by amidopyrine in cases of infection. Powdered opium produced several hours of drowsiness and relaxation and a distinct drop in the temperature level for several hours.

*Comment*—The cause of the elevated temperature and symptoms in this case is uncertain. The patient appears to be neurotic as well as ill, although the results of blood studies and the sedimentation time did not indicate the presence of an infection. The response of the fever to an antipyretic drug further suggested that the fever was of infectious origin.

The effect of doses of antipyretics and opiates similar to those administered to the patients just discussed was tested on several patients suffering from known infections and on one with Hodgkin's disease. A woman with chronic ulcerative colitis whose temperature reached 39.5 C (103 F) or 40 C (104 F) daily for several weeks was given 1.2 Gm of amidopyrine between 6 and 9 a m during the period in which increase of fever usually occurs. The temperature, having reached 38.4 C (101 F) at 8 a m, dropped rapidly to 36.8 C (98.2 F) and remained at 37 C (98.6 F) until 2 p m, increasing to 37.4 C (99.4 F) at 6 p m. Sodium phenobarbital in a dose of 0.36 Gm by mouth was given on another day at 9 a m and again at noon. The patient slept from 1 to 4 p m. The temperature reached 39.3 C (102.8 F) at noon, dropped to 38.3 C (101 F) at 4 p m and rose to 39.5 C (103 F) at 6 p m.

A man with undulant fever whose temperature fluctuated between a normal level and 38.3 C (101 F) daily for several weeks was given 0.6 Gm of amidopyrine at 8 and 10 a m. The temperature which had begun its usual ascent at 8 a m dropped promptly and descended to 36.2 C (97.2 F) at 5 p m (chart 5). On another day 0.14 Gm of powdered opium given at 8 a m apparently prevented the temperature from reaching its usual height for most of the day. Almost identical results were observed in a patient with Hodgkin's disease with fever of long duration.

#### DIAGNOSIS

In separating cases of "habitual hyperthermia" or "neurosis with long-continued low grade fever" from cases of fever due to infection, hyperthyroidism, intracranial disease and other causes, it is obvious that no single group of symptoms, signs, laboratory data and tests suffices

After ruling out organic disease of any nature by an accurate record of the history, long careful observation, repeated examinations and all the technical means available, it is necessary to consider the picture as a whole. There appear to be persons whose temperature is normally above the average accepted level of 37 C (98.6 F) without other symptoms, signs or complaints, who can be regarded as having genuine habitual hyperthermia. Regarding the neurotic person it is questionable whether the term habitual hyperthermia is desirable since the fever is usually a minor symptom or sign among others of greater concern to the patient, notably various evidences of exhaustion of the vegetative nervous system and vasocardiac and neuro-endocrine disturbances. In cases of this type it is highly desirable to determine the point at which to cease further search for an underlying pathologic process to avoid aggravating the neurosis, if present, and to avoid unnecessary enforced invalidism and expense. It appears to be largely a matter of judgment as to when a patient should be told to disregard the abnormal temperature and to lead a normal life.

There are a number of factors and data which are helpful in arriving at a diagnosis. The patients usually appear to be well physically and according to all objective signs except the fever, but they are often of the type regarded as neurotic. There are frequently signs of emotional and vasocardiac instability, with labile pulse, cold hands and feet, irritability, depression, hypochondria and other features illustrated in the four cases reported. In case 1 neurotic symptoms were insignificant, but in the others they were outstanding. None of the patients were aware of fever, in case 1 the temperature was the only feature which concerned the physicians and the relatives. The weight remained practically unchanged. All four patients were unmarried women.

*Temperature*—Although numerous readings are continually above the average normal, the temperature seldom exceeds 37.8 C (100 F), which may be considered the upper limit of normal, and remains regulated more or less constantly for years. Temperature curves exhibiting occasional high peaks with chills or chilliness, long wavelike periods at a high level and a low level alternately or other irregularities are indicative of an underlying organic process, infectious or otherwise. The extreme fluctuations between temperature readings for the day and those for the night in the cases reported were considerably greater—from 1.2 C (2.2 F) to 2 C (3.6 F)—than those observed in normal persons—0.8 C (1.5 F) to 1 C (1.8 F)—which is further suggestive of vasomotor or nervous lability.

*Drug Tests*—According to Holló and Holló-Weil<sup>8</sup> the effects of certain drugs on the temperature are diagnostic criteria. They were used with apparent success in the cases reported here. In each patient

large doses of amidopyrine, isopropylantipyrine, sodium salicylate and quinine failed to lower the temperature. Resistance to antipyretic drugs is characteristic of a normal temperature, in contrast to the reaction of fever of infectious origin. Unfortunately for diagnostic purposes, fever due to organic brain disease is also uninfluenced by these drugs<sup>12</sup>. The effect of opium, morphine, avertin, phenobarbital and sodium amytal in lowering the temperature during the period of narcosis further suggests the rôle played by nervous stimulation in the regulation of temperature in this type of patient. The effect of relaxation is shown by the low levels of temperature attained at night during natural sleep. Sedative drugs, however, were of less diagnostic value than the antipyretic drugs since the temperature in some cases of infection (chart 5) was also somewhat reduced by induced narcosis. It is necessary to repeat the drug tests at intervals to avoid misinterpretation due to occasional irregularities of the temperature curve.

Certain "antispasmodic" drugs had no effect on the temperature curve in the cases studied. Epinephrine failed to cause the striking increase of fever noted by Cawadias<sup>10</sup> in any of the patients reported on here. Thyroid extract had no effect on the temperature in case 2. Physical exercise caused a distinct rise in temperature in case 1 but not in cases 2, 3 or 4. Emotional excitement was especially effective in increasing the temperature in cases 1 and 2 but had little effect in cases 3 and 4. The injection of typhoid vaccine intravenously caused a normal response with chill and fever in cases 3 and 4.

*Studies of the Blood*—Numerical and morphologic changes in the numbers of leukocytes are of importance in ruling out infectious and blood diseases. Marked shifts to the right or left in the hemogram and evidence of toxicity in the cells are indicative of infection or of organic disease. Slight shifts or other changes are of little significance since they occur in normal persons and occasionally during actual infections. The red blood cell count and hemoglobin content are usually normal. Mild secondary anemia was corrected in two cases without influencing the temperature curve.

The sedimentation time of the blood was at one time believed to be of great value in differentiating infectious from noninfectious disease. Unfortunately the test is not always reliable. The rate may be increased in noninfectious disease<sup>13</sup> and may be normal in undulant fever<sup>14</sup> and

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12 De Lange, C. Fieber von 6½ jähriger Dauer bei einem Kinde mit angeborenen Missbildungen des Gehirns und Rückenmarks und angeborenem Tumor Medullae, *Acta pædiat* **14** 503, 1933.

13 Reimann, H. A. Hyperproteinemia as a Cause of Autohemagglutination, *J. A. M. A.* **99** 1411 (Oct 22) 1932.

14 Curschmann, H. Ueber die diagnostische Bedeutung der Senkungsreaktion bei akuten Infektionskrankheiten, *München med. Wchnschr.* **45** 1767 (Nov 10) 1933.

in other infections. It was normal in cases 1, 2, 3 and 4 and in case 5 in which the fever was regarded as of infectious origin.

Agglutinins for typhoid, paratyphoid, undulant fever and tularemia when present in high titer are indicative of the respective disease. The titer of the agglutinins in question was nil or insignificant in my cases.

*Intradermal Tests*—The intradermal tests for undulant fever, tularemia and tuberculosis are of value in ruling out infection when the reaction is negative and in supporting a diagnosis when the reaction is strongly positive. Indefinite reactions are often confusing and of no significance. The reaction to tuberculin was positive in cases 2 and 3, but no other evidence of tuberculosis was found.

*Basal Metabolism*—The basal metabolic rate is increased in hyperthyroidism and in cases of fever of infectious origin. The rate was within normal limits in each of my four patients even when the temperature was elevated. The rate may also be normal during fever caused by brain lesions, which lessens its diagnostic value in the type of case under discussion. Chemical studies of the blood in my cases failed to indicate metabolic disturbances.

#### TREATMENT

The patients were informed that no dangerous cause existed for their complaints and fever and that certain persons normally have elevated temperature. With this assurance they were advised to lead a normal life and to disregard the symptoms. For a certain type of person this direction is difficult to follow, as is illustrated in cases 2 and 3 in which the patients sought further advice elsewhere. Psychotherapy and occupational therapy to divert interests were of considerable success in cases 2 and 4. Each patient was urged to return for reexamination at least once or twice a year.

#### SUMMARY

A careful study of four cases failed to reveal any organic basis for prolonged low grade fever known to have existed for at least twenty-one, six, seven and fourteen years, respectively. The table shows the variations expected in a population and indicates the wide normal range of temperature, with the extremes at 36.1 C (97 F) and 38 C (100.4 F). Statistical analysis of the records of temperature of the four patients indicates that in each the range fell well within the limits of normal. The temperature in certain normal persons may be regulated slightly above the usually accepted normal level, and in some persons of a neurotic nature the elevated temperature is one of the signs of their abnormal constitutional type together with other evidence of vasocardiac and nervous instability. It is important to realize that persons of this nature are not rare and that once the condition is recognized

further useless search for an underlying pathologic process is obviated and proper guidance can be undertaken. The condition should be regarded as a neurosis or as habitual hyperthermia only after thorough and prolonged examination fails to reveal an organic basis. There are no infallible criteria for determining a diagnosis. Each case must be regarded individually. Certain data helpful in establishing a diagnosis are discussed, but the picture must be regarded as a whole, with especial emphasis on the constitutional type of person, the nature of the symptoms and signs, the constancy of the temperature, the absence of evidence of infection or other organic disease, the constancy of weight, the normal metabolism and the response to antipyretic and narcotic drugs.

# INITIAL ATTACKS OF RHEUMATIC FEVER IN PATIENTS OVER SIXTY YEARS OF AGE

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AND

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Within the past few years initial attacks of rheumatic fever have been observed with surprising frequency in the Boston City Hospital in patients past middle life, and in six instances in patients over 60 years of age. Since initial attacks of rheumatic fever are generally considered to occur in childhood or in early adult life, such a diagnosis in patients past middle life necessarily requires rigid criteria, however, when one encounters in an elderly patient with polyarthritis electrocardiographic changes consistent with rheumatic fever, in addition to other rheumatic manifestations, the diagnosis should be strongly entertained.

In cases of elderly patients with polyarthritis the diagnosis of rheumatic fever is often dismissed largely because of the age of the patient. For this reason and because initial attacks of rheumatic fever are rarely described in elderly people, we are reporting the six cases in which we believe the first attack occurred after the age of 60.

Of these six patients, three died, and the diagnosis of rheumatic fever was confirmed at autopsy. In the cases with recovery the diagnosis was based on the presence of polyarthritis, together with active cardiac involvement, such as pericarditis, endocarditis and fluctuating disturbances of the conduction system in the heart, and a clinical course consistent with the disease. It is difficult to determine whether a given attack represents the onset of rheumatic fever, but in the absence of a history of previous involvement of the joints or other rheumatic manifestations and with the lack of clinical evidence of rheumatic heart disease, such an assumption is justified.

## REPORT OF CASES

CASE 1—I B, a 79 year old American widow, was admitted to the hospital complaining of pain in the joints. Two weeks before admission pain and swelling developed in the right hand, the right shoulder and both wrists following a "head cold." For six months she had occasional fleeting pains in the wrists and shoulders. There was no history of rheumatism or chorea.

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On physical examination the patient was found to be comfortable in the horizontal position, and respirations were 20 per minute. The borders of the heart could not be measured because of obesity. The cardiac rate was 100 beats per minute, and premature beats were frequently detected. A medium-pitched systolic apical murmur was heard, and at times a suggestive gallop rhythm was detected. The systolic blood pressure was 130 mm of mercury, and the diastolic, 80 mm. The lungs were clear except for a few coarse moist râles at the base of each lung. Swelling, tenderness and local heat were present in the left hand and in both wrists, and there was pain on motion in both ankles and in the left shoulder. The temperature was 100.6 F. The remainder of the examination revealed conditions essentially within normal limits for a person of the patient's age.

Examinations of the urine revealed nothing abnormal. The hemoglobin was 60 per cent (Sahli), and the erythrocytes numbered 3,500,000 per cubic millimeter of blood and the leukocytes, 15,800, 84 per cent of which were polymorphonuclear neutrophils. The red blood cells showed moderate achromia. The nonprotein nitrogen of the blood was 60 mg per hundred cubic centimeters. The Kahn reaction of the blood was negative. Roentgen examination revealed clear pulmonary fields and a slightly enlarged heart. The electrocardiogram showed a normal sinus rhythm but a prolonged conduction time, the P-R interval being 0.24 second.

Soon after admission the temperature fell to 99 F, and the severity of the symptoms in the joints lessened, but the leukocyte count remained between 16,000 and 20,000 per cubic millimeter. Intractable vomiting and abdominal distention developed, and on the seventh day after admission the temperature rose rapidly to 102.4 F, and the respiratory rate increased. The patient died twenty-four hours later.

Postmortem examination revealed a hypertrophied heart weighing 410 Gm, with some thickening of the free edges of the mitral and tricuspid leaflets but with no resulting deformity and no shortening of the chordae tendineae. The aortic and pulmonary valves were normal. There was no gross abnormality of the myocardium or endocardium. Some sclerosis of the coronary arteries was present. The remainder of the examination revealed the following abnormalities: congestion of the lungs and liver, bilateral healed pleuritis, old healed peritonitis with many fibrous adhesions, chronic cholecystitis and cholelithiasis, cysts of the right ovary, benign nephrosclerosis and slight arteriosclerosis.

Histologic examination of the myocardium revealed numerous well formed typical Aschoff bodies. There was no evidence of old rheumatic lesions.

Whereas the clinical and electrocardiographic findings were consistent with the diagnosis of rheumatic fever, this diagnosis was questioned on account of the patient's advanced age. Death was apparently the result of myocardial failure.

CASE 2—E. R., a 65 year old Syrian merchant, was admitted to the hospital complaining of sudden pain in the right side of the thorax and weakness of two weeks' duration. These symptoms were accompanied by shortness of breath and dizziness and were followed within a few hours by a cough productive of blood-tinged sputum. During this illness the patient had fever and profuse sweats. No history of symptoms in the joints was obtained.

On examination the patient was dyspneic, and the respiratory rate was 40 per minute. Percussion revealed a slightly enlarged heart, the left border being 10 cm from the midsternal line in the fifth intercostal space. The cardiac rate was 100 beats per minute, and on auscultation a rapid tick-tack rhythm was heard. Dropped beats occurred frequently, the normal beat being replaced by a distant, rumbling sound, which was interpreted to be the auricular systole. The systolic blood pressure was 115 mm of mercury, and the diastolic 78 mm. Examination

of the lungs revealed dulness at the base of the right lung and diminished voice conduction over the same area, a few fine râles were present. The temperature was 101.6 F.

The urine was essentially normal. The hemoglobin was 70 per cent (Sahli), and the leukocytes numbered 11,700 per cubic millimeter. The Kahn reaction of the blood was negative. Roentgen examination of the lungs suggested either fluid or consolidation at the base of the right lung, but repeated thoracenteses produced no fluid. Unfortunately, electrocardiographic tracings were not obtained.

The patient's condition rapidly improved following admission, and the temperature reached normal on the fifth day. After seven more days he was well enough to be out of bed, but the marked weakness continued, and the pulse rate remained elevated, ranging between 100 and 110 beats per minute. During this time he complained of pain in the left shoulder, which was relieved by the local application of methyl salicylate. Three weeks after admission the temperature rose again, the respiratory rate increased, and pain developed in the left axilla. Over this area a pleural friction rub was heard, and dulness and diminished voice conduction were also present. These symptoms and signs subsided within a few days. Ten days after the attack, however, while the patient was in bed, excruciating pain suddenly developed over the precordium, accompanied by marked respiratory distress, and he died within a few hours.

At autopsy the heart was small (245 Gm.) and appeared grossly normal save for atherosclerotic plaques at the bases of the mitral, aortic and pulmonic valves and moderate sclerosis of the coronary arteries. No valvular pathologic process was found.

Other abnormal changes were pulmonary infarcts, obliteration of both pleural cavities by fresh and old fibrous adhesions, acute splenitis, benign nephrosclerosis, benign hypertrophy of the prostate and generalized arteriosclerosis.

Microscopically, several typical Aschoff bodies were present in the section of myocardium. No old lesions were noted.

In this case the symptoms and death were the result of pulmonary infarction. Because of the small degree of involvement of the joints and because of the patient's age the diagnosis of rheumatic fever was not considered clinically, and the cardiac abnormalities were attributed to arteriosclerotic heart disease.

CASE 3—E. E., a 61 year old white machinist, had been in good health until two weeks before admission, at which time a "head cold" developed, which was followed within seven days by pain in the shoulders, back and knees. Three days before admission he became dyspneic, and a paroxysmal cough developed, these symptoms became increasingly severe up to the time of admission. There was no history of involvement of the joints or of chorea.

Physical examination revealed an obese man with obvious dyspnea and orthopnea. The respiratory rate was 40 per minute. There was slight cyanosis of the lips. The heart was enlarged to the left, percussion revealed the left border of dulness 12 cm. from the midsternal line in the fifth intercostal space. The cardiac rate was 110 beats per minute, the sounds were of fair quality. Over the apical region a loud blowing systolic murmur was heard. The systolic blood pressure was 140 mm. of mercury, and the diastolic, 78 mm. The radial arteries were thickened. Examination of the lungs revealed an asthmatic type of breathing, with musical and sonorous râles present throughout both lungs. There was pain on motion in both knees and shoulders and moderate pitting edema of the ankles. The temperature was 98.6 F.

The urine contained a large trace of albumin and an occasional red blood cell in the sediment. The hemoglobin was 40 per cent (Sahli), and the leukocyte



count was 7,500 per cubic millimeter. The nonprotein nitrogen of the blood was 60 mg per hundred cubic centimeters. The Kahn and Wassermann reactions of the blood were negative.

Although the temperature remained normal, the symptoms in the joints increased, and the respiratory rate became elevated. On the fifth day following admission the temperature rose, the patient coughed up blood-streaked sputum, and signs of consolidation developed at the base of each lung. He lapsed into coma and died on the following day.

At autopsy there was slight hyaline and fibrous scarring of the pericardium. The heart was enlarged (650 Gm.), with distention on the right side. The myocardium was mottled with yellow and brown. The tricuspid, pulmonary and aortic valves were normal save for a small petechial hemorrhage in one leaflet of the tricuspid valve. The mitral valve was slightly thickened, and minute firm granulations suggesting rheumatic lesions were present on an area 1 cm. in length. There was sclerosis of the coronary arteries and of the aorta at the level of the coronary orifices, and a nodule measuring 3 mm. extended into the lumen at this point.

In addition to these observations there were pulmonary congestion and edema, passive congestion of the liver, spleen and kidneys, resulting from cardiac failure, bronchopneumonia, benign nephrosclerosis, and marked arteriosclerosis throughout the aorta.

Microscopically, numerous typical Aschoff bodies were scattered throughout the myocardium. All these appeared to be of recent origin.

The clinical diagnosis of rheumatic fever was questioned because of the patient's advanced age. The outstanding clinical symptoms were referable to the joints and to the heart. There was evidence of myocardial failure both clinically and at postmortem examination, but death was the direct result of terminal bronchopneumonia. We were unable to decide whether the cardiac hypertrophy was due to arteriosclerosis or was related to the rheumatic disease.

CASE 4—J. O., a 62 year old cabinetmaker, had had intermittent attacks of polyarthritis accompanied by fever for one year previous to admission, during which time the family physician had observed the appearance of signs of mitral stenosis. The patient had steadily lost weight and had become progressively weaker. Two days before admission a sharp, stabbing pain over the precordium and a dry cough developed. Except for having had typhoid fever at the age of 21, the patient had always been in good health. No history of rheumatism or chorea was obtained.

Physical examination revealed moderate emaciation and some pallor of the skin. On percussion the heart appeared normal in size. The cardiac rate was 100 beats per minute, and premature beats occurred frequently. A loud systolic and presystolic murmur were heard over the mitral area of the heart. The systolic blood pressure was 130 mm. of mercury, and the diastolic, 90 mm. Examination of the extremities revealed swelling, local heat and tenderness of both knees and pain on motion in the left shoulder and in both wrists and ankles. The temperature was 99.6 F.

Examination of the urine revealed an occasional hyaline cast. The hemoglobin was 80 per cent (Sahli), and the leukocyte count 14,000 per cubic millimeter, with 78 per cent polymorphonuclear neutrophils. The nonprotein nitrogen of the blood was 36 mg per hundred cubic centimeters, and the uric acid, 21 mg. The Kahn reaction of the blood was negative. Three blood cultures remained sterile. Roent-

gen examination showed the lungs to be normal. The initial electrocardiographic tracing showed a prolonged P R interval of 0.24 second, the axis was normal.

Following admission the temperature remained elevated, varying from 100 to 102 F. The symptoms in the joints persisted in spite of the administration of 120 grains (7.7 Gm) of sodium salicylate daily. The leukocyte count remained at about 10,000 per cubic millimeter.

During the fourth week the patient showed clinical evidence of pericarditis, pleuritis and patchy areas of consolidation in the lungs, the latter being verified by roentgen examination. These severe manifestations lasted approximately five weeks. During this period the symptoms in the joints, fever and leukocytosis continued, and moderately severe anemia developed, the hemoglobin content falling to 52 per cent and the erythrocyte count to 2,900,000 per cubic millimeter. The patient complained continually of marked prostration and weakness.

The fever gradually subsided, and the leukocyte count became normal. Occasional pains in the joints persisted in spite of the administration of salicylates, however, and the patient continued to complain of marked weakness.

Changes in the cardiac rhythm and the conduction time, as noted in electrocardiographic tracings, were striking. At the time of admission there was partial heart block, with a P R interval of 0.24 second. During the period in which pericarditis was present there was a transient auricular fibrillation. Several weeks later the P R interval returned to the normal time of 0.16 second. During the latter part of the patient's stay in the hospital frequent tracings showed it to vary between 0.25 and 0.22 second.

Six months after admission the patient was discharged to a convalescent home improved, but with active carditis still present, as evidenced by an abnormally high pulse rate and prolongation of the P R interval.

In this case the outstanding symptoms and signs were referable to the joints. The clinical course was that of fulminant rheumatic fever, with pancarditis, pleuritis and pneumonitis. Rapidly progressive anemia and marked prostration and weakness were the outstanding features. The diagnosis was based on the occurrence of polyarthritis, together with signs of pancarditis, prolonged abnormal variation in the conduction time and the development of mitral stenosis. Failure to obtain a history of rheumatic fever, the absence of cardiac enlargement and the observation that the valvular lesion had developed during this illness constitute the evidence that this was a first infection. The failure of the manifestations in the joints to respond to salicylate therapy is not unusual in the presence of involvement of the lung and pleura.<sup>1</sup>

CASE 5—A 65 year old unemployed man was admitted to the hospital complaining of pain in the chest and pain and swelling in the joints. Four weeks previously he had a sore throat, followed within two weeks by pain in the right side of the thorax, which was accentuated by respiration, and pain and tenderness in the ankles and toes. No history of symptoms suggestive of previous rheumatic fever or chorea was obtained.

On physical examination the patient was found to be undernourished and pale but except for weakness was comfortable. On percussion the heart appeared to be normal in size. The rate was 100 beats per minute, there was an occasional premature beat. No murmur or pericardial friction rub was heard. The systolic blood pressure was 120 mm of mercury, and the diastolic, 75 mm. The radial

1 Myers, W. K., and Ferris, E. B., Jr. Pleurisy in Rheumatic Fever, *Arch Int Med* 52:325 (Aug) 1933.

arteries were palpable. There was tenderness on heavy percussion along the tenth rib in the right axilla, and over this area a pleural friction rub was heard, otherwise the lungs appeared to be normal. There were redness, tenderness and some swelling of the first tarsometatarsal joints and of the right ankle, the left knee was painful on motion. The temperature was 99 F.

The urine was normal. The hemoglobin was 80 per cent (Sahli), the erythrocytes numbered 4,560,000 per cubic millimeter, and the leukocytes, 7,700. The uric acid of the blood was 37 mg per hundred cubic centimeters, the Kahn reaction was negative, and the erythrocyte sedimentation rate was very rapid. Roentgen examination revealed no abnormalities in the pulmonary fields, in the heart shadow or in the inflamed joints. Electrocardiographic tracings revealed an abnormally increased auriculoventricular conduction time of 0.24 second, otherwise the rate was within normal limits.

One week after admission the pleural friction rub disappeared, and the manifestations in the joints subsided, except for slight pain in the knees and toes. The course following admission was characterized chiefly by progressive weakness and anemia, the hemoglobin fell to a minimum of 42 per cent, and the erythrocytes to 2,650,000 per cubic millimeter, in spite of the administration of 6 Gm of iron and ammonium citrate daily. Percussion revealed an enlarged heart, and an apical systolic murmur developed, which gradually increased in intensity. The temperature remained around 99 F, with occasional elevations to 100 F. The leukocyte count varied between 5,000 and 14,000 per cubic millimeter. The corrected erythrocyte sedimentation rate continued to be rapid.

During the fifth month after admission a painful swelling developed over the fourth metacarpophalangeal joint of the right hand, accompanied by tenderness and an increase of local temperature. At this time a tentative diagnosis of rheumatic fever was made, and the patient was given 120 grains of sodium salicylate daily in divided doses. All the manifestations in the joints subsided immediately, and the patient felt greatly improved. The corrected erythrocyte sedimentation rate returned subsequently to normal, and although the administration of iron had been discontinued, the erythrocyte count and the hemoglobin content steadily rose. On the patient's discharge, eight months after admission, the hemoglobin was 63 per cent, and the erythrocytes numbered 4,800,000.

Electrocardiographic tracings taken at intervals revealed striking changes in the cardiac conduction time. On admission the P R interval was 0.24 second, and the same figure was observed three weeks later. During the seventh week a heart block with a ratio of 2:1 between the rate of the ventricles and that of the auricles was observed, which was soon followed by complete auriculoventricular dissociation. Later the P R interval decreased to 0.24 second and at the time of discharge was within normal limits (0.19 second).

In this case the outstanding symptoms were severe prostration and weakness. The diagnosis was based on the occurrence of polyarthritis, together with prolonged and variable changes in the cardiac conduction time, and also on the prompt response to salicylate therapy. The assumption that this was the initial attack was based on the absence of a history of rheumatic fever, the absence of evidence of valvular disease and the fact that the heart was normal in size on admission.

CASE 6—A M., a 63 year old cabinetmaker, was admitted to the hospital because of pain in the joints. Three weeks before admission pain and swelling developed in the left elbow, which were followed within a few days by migratory

arthritis in all the large joints, as well as in the fingers and toes. No history of previous symptoms in the joints or of other rheumatic manifestations could be obtained.

Physical examination revealed a well nourished elderly man in no acute distress. On percussion the heart appeared to be normal in size. The cardiac rate was 100 beats per minute, the sounds were of good quality, and no murmurs or rubs could be heard. The systolic blood pressure was 130 mm of mercury, and the diastolic, 80 mm. The lungs were normal. There was redness, increased temperature and tenderness of the right elbow and knee and of both ankles. There was pain on motion in the right wrist and in both shoulders. The temperature was 101.8 F. The other findings were within normal limits for a person of the patient's age.

The urine contained only a few leukocytes and an occasional granular cast. The hemoglobin was 70 per cent (Sahli), the erythrocytes numbered 3,470,000 per cubic millimeter, and the leukocytes, 22,300, 87 per cent being polymorphonuclear neutrophils. The corrected erythrocyte sedimentation rate was very rapid. Roentgen examinations of the lungs, heart and joints gave negative results. An electrocardiographic tracing was within normal limits, except for a P-R interval of 0.24 second.

Following the administration of 120 grains of sodium salicylate daily in divided doses, the patient showed rapid clinical improvement. The symptoms in the joints subsided within a few days, and the temperature and leukocyte count fell to normal levels after three weeks. Salicylate therapy was discontinued for three days during this period, and the symptoms in the joints promptly returned. Two months after admission a series of severe nosebleeds developed when the patient was allowed to be out of bed. At the time of writing, six months after admission, the patient is free from symptoms, except for fleeting pains in the joints.

Electrocardiographic tracings taken from time to time showed marked fluctuation of the cardiac conduction time. The P-R interval was 0.24 second on admission, 0.28 second two weeks later and 0.22 second at the end of one month. It later reached a minimum of 0.16 second and then varied from 0.2 to 0.24 second until the sixth month following admission, when it returned to 0.18 second.

In this case the symptoms and course were prolonged but relatively mild. The diagnosis was based on the occurrence of polyarthritis in association with variations in the cardiac conduction time, the response of the joints to salicylates and other manifestations of rheumatic fever, such as fever, leukocytosis and epistaxis. It appeared to be an initial attack because of the evidence on admission of a normal-sized heart without valvular disease and the absence of a history of previous rheumatic infection.

#### COMMENT

It seems evident that each of these six patients was suffering from an initial attack of rheumatic fever. The patients who recovered gave no history suggestive of previous rheumatic infection, nor was there any evidence of valvular disease or cardiac hypertrophy at the time of onset. Those who died presented no evidence of previous infection either clinically or at postmortem examination. Von Glahn and Pappenhimer,<sup>2</sup> in a study of ten cases of rheumatic fever in which the

<sup>2</sup> Von Glahn, W. C., and Pappenhimer, A. M. Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am J Path* 2:235 (May) 1926.

patients came to autopsy, reported one case of a patient who similarly had the first attack after the age of 60

In our cases 5 and 6 the significance of the electrocardiographic changes in the diagnosis of rheumatic fever may be open to question, particularly in view of the age of the patients and the absence of other evidence of cardiac involvement. In patients with hypertensive or coronary heart disease abnormal auriculoventricular conduction time, when present, is usually permanent and progressive and, as a rule, does not fluctuate or return to normal. Transient prolongation of the P R interval was observed in many cases of acute infection by Master and his co-workers<sup>3</sup>. In these two patients, however, abnormal changes in the auriculoventricular conduction time persisted long after the temperature and the leukocyte count became normal. In the four other cases there can be little doubt as to the diagnosis. In cases 1, 2 and 3 typical Aschoff bodies were found in the myocardium at autopsy, in case 4 signs of mitral stenosis developed, and there was other obvious evidence of carditis in addition to the electrocardiographic records.

The signs and symptoms of rheumatic fever in these patients were essentially the same as those encountered in younger patients, with the possible exception that on the average the manifestations in the joints were less intense but more prolonged. The course of the disease appears to be just as chronic as in younger persons with a comparable degree of cardiac involvement. Of the three patients who survived, all showed evidence of active carditis for approximately six months.

In studies of the age incidence of rheumatic fever various clinicians<sup>4</sup> noted its occurrence in elderly patients in a significant percentage of cases, they presented little conclusive evidence, however, to support the diagnosis. During the past five years, of fifty-eight patients<sup>5</sup> who were admitted to the second and fourth medical services who were considered to have their first attack of rheumatic fever and who presented definite evidence of active carditis, 45 per cent were 30 years of age or older, and 17 per cent were over 40.

Although the incidence of rheumatic fever is relatively low in patients past middle age, we believe that it occurs with sufficient fre-

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3 Master, A. M., Romanoff, A., and Jaffe, H. Electrocardiographic Changes in Pneumonia, *Am Heart J* **6** 696 (June) 1931. Master, A. M., and Jaffe, H. Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, *Proc Soc Exper Biol & Med* **31** 931 (May) 1934.

4 Lambert, A. The Incidence of Acute Rheumatic Fever at Bellevue Hospital, *J A M A* **74** 993 (April 10) 1920. Rolly, F. Der akute Gelenkrheumatismus, Berlin, Julius Springer, 1920. Mackie, T. T. An Analytical Study of Three Hundred and Ninety-Three Cases of Rheumatic Fever and Eighty-Nine Cases of Chorea, *Am J M Sc* **172** 199 (Aug.) 1926.

5 Only patients over 12 years of age are admitted to the medical services.

quency to warrant its careful consideration in all patients of that age with polyarthrititis

#### CONCLUSIONS

Six cases of patients over 60 years of age with first attacks of rheumatic fever are reported. In three cases the diagnosis was confirmed at autopsy.

The course of the disease is similar to that in younger persons, except that the manifestations in the joints are possibly less intense and more persistent.

In older patients with polyarthrititis rheumatic fever should be considered as a diagnostic possibility.

# NOTES ON PERNICIOUS MALARIA

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Malaria remains a hazard of great importance in areas where impounded water is abundant and the breeding season of *Anopheles* is long. The high morbidity and mortality rates from malarial infection in areas in which the disease is endemic have been adequately demonstrated by epidemiologic surveys of typical zones<sup>1</sup>. The purpose of the present report is to review certain observations made on hospitalized patients with malaria during the past fifteen years in an area along the Savannah River. The cases are cited as examples of neglected infection with more or less alarming symptoms. Simple malarial infections have been cared for as a routine in the outpatient department and are not considered.

From Jan 1, 1919, to Jan 1, 1934, a total of 814 patients with a clinical diagnosis of malaria have been admitted to the University Hospital. On examination of 38 of the patients, most of whom had taken antimalarial remedies, no parasites were found in the blood, and in 76 instances the species of parasite found in the blood was not recorded. In 198 of the remaining 700 patients, the infection was proved to be of the tertian, and in 502 it was of the estivo-autumnal variety. Mixed infection occurred in 2 patients with the estivo-autumnal type of the disease, and double infection was not uncommon in patients with tertian malaria.

The largest number of proved cases of malaria occurred in white male patients, as shown in table 1. Differences in incidence according to race in the estivo-autumnal group may be accounted for by unequal racial distribution of the hospital population. However, the disparity in the tertian group is even greater, the white outnumbering the Negro patients by 70.5 per cent. According to figures furnished by the bureau of public health, more than 70 per cent of the cases of malaria in the

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1 Bass, C. C. Prevalence of Malaria and Its Control by Treating Carriers, *South M. J.* **12** 190 (April) 1919. Craig, C. F. The Malarial Fevers, Hemoglobinuric Fever and the Blood Protozoa of Man, New York, William Wood & Company, 1909. Deaderick, W. H. A Practical Study of Malaria, Philadelphia, W. B. Saunders Company, 1909.

community during the past five years have occurred in white persons, although the population is made up of almost equal numbers of members of the two races. Further evidence of greater resistance on the part of the Negroes was observed in patients with cerebrospinal syphilis treated with tertian malaria. Only 30 per cent of the Negro, as compared with 90 per cent of the white, patients were infected by the first therapeutic inoculation.

The seasonal incidence of cases of tertian and estivo-autumnal malaria was characteristic, as depicted in the chart. The curve for pernicious malaria attained a peak simultaneously with that for estivo-

TABLE 1—*Incidence and Mortality Rate According to Race and Sex in 198 Cases of Tertian and in 502 Cases of Estivo-Autumnal Malaria*

	Race	Sex	Number of Cases	Number of Deaths	Mortality Rate, Percentage
Tertian malaria	White	Male	90	0	0.00
		Female	79	1	1.26
	Total		169	1	0.59
	Negro	Male	22	0	
		Female	7	0	
	Total		29	0	0.00
Total			198	1	0.50
Estivo autumnal malaria	White	Male	201	20	9.95
		Female	130	14	10.85
	Total		331	34	10.27
	Negro	Male	126	12	9.52
		Female	45	4	8.88
	Total		171	16	9.35
Total			502	50	9.98

autumnal malaria, in October. Cases occurring in the winter were regarded as instances of inadequately treated infections carried over from the preceding season.

The mortality rates for the whole group as given in table 1 were largely proportional to the occurrence of pernicious malaria. Of the total 51 deaths, 47 resulted from a pernicious estivo-autumnal infection. In the other 4 fatal cases malaria perhaps acted as the exciting cause of death in the presence of chronic cardiovascular disease. The fatal case in the tertian group was that of a middle-aged woman with hypertension and albuminuria who died of renal failure. In the estivo-autumnal group, a man aged 55 with hypertensive vascular disease died of congestive cardiac failure, and 2 men aged 65 and 87, with arteriosclerosis, died of uremia.



## INCIDENCE AND CHARACTERISTICS OF PERNICIOUS MALARIA

Pernicious manifestations occurred in 97 cases, or 19.32 per cent, of the estivo-autumnal group (table 2). Symptoms of comparable severity from a clinical standpoint were not observed in tertian malaria.

Pernicious malaria generally developed as a rather sudden complication of an inadequately treated estivo-autumnal infection with a progressive course. Most patients with pernicious malaria had in the beginning ague, fever, malaise or other symptoms typical of an advancing estivo-autumnal infection. The degree of anemia, icterus, elevation of temperature and splenic enlargement was, as a rule, greater in the cases in which pernicious malaria developed. It will be seen that such

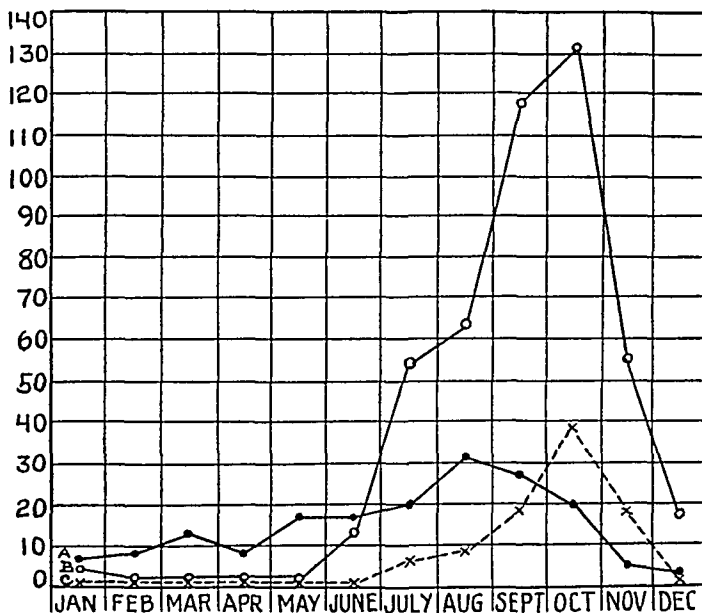


Chart showing the incidence by months of 198 cases of tertian, 502 cases of estivo-autumnal and 97 cases of pernicious malaria occurring over a period of fifteen years. A is the curve for tertian, B, for estivo-autumnal, C, for pernicious, malaria.

cases had certain distinctive prodromes in common and, in addition, presented the classic features which serve to characterize the individual clinical types of the disease.

*Cerebral Type*—Of the 97 pernicious cases, 75, or 77.3 per cent (14.96 per cent of the estivo-autumnal group), were of the cerebral type (table 2). Fifty-six, or 74.6 per cent of the cases of cerebral malaria occurred in males and 36, or 47 per cent, in Negroes. Moreover, all but 1 of the cases of pernicious malaria in Negroes were of the cerebral type.

Particular symptoms were observed in the cases of the cerebral type with noteworthy frequency, although the records for comatose patients were often incomplete. Severe persistent headache introduced the pernicious stage in 45 of 49 cases in which complete histories were available. Delirium was definitely the initial pernicious manifestation in 48 of the 49 cases. Nausea and vomiting occurred before or during the phase of delirium in 27 of 35 cases in which specific notations were made. Sudden convulsion was the first pernicious symptom noted in 1 adult with chronic alcoholism and in 6 of 15 children below the age

TABLE 2—*Incidence of Pernicious Malaria in 502 Cases of Estivo-Autumnal Infection*

Clinical Type	Number of Cases	Percentage of Pernicious Malaria	Percentage of Estivo Autumnal Malaria
Cerebral	75	77.3	14.94
Hemorrhagic	16	16.5	3.19
Algid	6	6.2	1.19
Total	97	100.0	19.32

TABLE 3—*Incidence and Mortality Rate According to Race and Sex in 75 Cases of Pernicious Cerebral Malaria*

Race	Sex	Number of Cases	Number of Deaths	Mortality Rate, Percentage
White	Male	23	12	42.8
	Female	11	8	72.7
	Total	39	20	51.3
Negro	Male	28	14	50.0
	Female	8	4	50.0
	Total	36	18	50.0
Total		75	38	50.6

of 10 years. At the time of admission, 58 of the 75 patients were in a state of profound coma. The other 17 patients were disoriented and stuporous, but they could be aroused and then gave evidence of a muttering delirium. Dehydration was uniformly extreme, and anemia, occult. Plasmodia, usually in large numbers, were found in the blood.

Recovery from the cerebral type of malaria apparently depended to the greatest extent on the degree and duration of the pernicious symptoms. The 17 patients who were semicomatose on admission all survived. Likewise, of 24 patients with a definite history who recovered from coma, none had been unconscious for longer than twenty-four hours. Another factor of importance in deciding the outcome of cerebral malaria seemed to be the relative number of parasites present in the blood. Of 45 patients in whose blood less than ten parasites per

oil immersion field were seen, 33 recovered, while 12 patients whose blood showed from 20 to 75 plasmodia per field, died

The results of treatment of 60 of the 75 patients with cerebral malaria are recorded in table 4. The remaining 15 patients were moribund on admission and succumbed within ten hours without having received specific treatment. No instances of recovery were frankly spontaneous, but the possibility that some were so appeared likely from the circumstances in several of the cases in which treatment was given. Quinine di-hydrochloride in doses of 0.5 Gm given in 200 cc or more of hypertonic dextrose solution at intervals of from six to eight hours was apparently life-saving in 10 cases of coma. Sodium cacodylate

TABLE 4—*Results of Therapy in 60 Cases of Pernicious Cerebral Malaria*

Specific Therapeutic Measures	Number of Cases	Number of Deaths	Mortality Rate, Percentage
Quinine, orally, and sodium cacodylate, intravenously	28	9	32.1
Quinine, orally and intramuscularly	12	4	33.3
Quinine, orally and intravenously	10	0	0.0
Sodium cacodylate, intravenously	9	9	100.0
Atabrine, orally	1	1	100.0
Total	60	23	38.3

TABLE 5—*Incidence and Mortality Rate According to Race and Sex in 16 Cases of Pernicious Hemorrhagic Malaria*

Race	Sex	Number of Cases	Number of Deaths	Mortality Rate, Percentage
White	Male	12	5	41.6
	Female	3	1	33.3
Negro	Male	1	0	0.0
Total		16	6	37.5

proved ineffectual when given alone or with quinine by way of the stomach. Under treatment with atabrine, a delirious patient became comatose and died within thirty-six hours.

*Hemorrhagic Type (Blackwater Fever)*—Sixteen, or 3.19 per cent, of the cases in the estivo-autumnal group were of the pernicious hemorrhagic type (table 2). A single instance of blackwater fever was observed in a Negro (table 5). Hemoglobinuria was marked in 15 and moderate in 1 of the cases. All the patients with hemorrhagic malaria gave negative reactions to the Wassermann test.

Intractible headache, nausea and vomiting were prodromal features in each case of hemorrhagic malaria. Severe chills definitely preceded or attended the onset of urinary discoloration in 11 cases. Darkness of the urine had been noted for less than forty-eight hours before admission by 14 of the 16 patients in whom it occurred. There was a history of repeated malarial infection in 12 and of previous blackwater

fever in 5 of the cases. Fourteen patients had taken quinine, or proprietary nostrums containing quinine, shortly before the onset of the hemoglobinuria. At the time of admission the patients were lethargic and prostrate. Delirium was present or developed later in 12 instances, and coma ensued in 4 of the 6 fatal cases. Anemia and icterus were decidedly more pronounced than in other types of pernicious malaria. Parasites were found in the peripheral blood in only 3 cases in which the patient had blackwater fever.

The results of therapy in 14 of the hemorrhagic cases are shown in table 6. Two moribund patients with blackwater fever who lived less than six hours after admission received no treatment other than supportive measures. Active hydration and purgation were employed in

TABLE 6—*Results of Therapy in 14 Cases of Pernicious Hemorrhagic Malaria*

Measures of Therapy	Number of Cases	Number of Deaths	Mortality Rate, Percentage
Sodium cacodylate, intravenously, and blood transfusion	7	2	28.5
Sodium cacodylate, intravenously only	2	2	100.0
Quinine, intramuscularly, and blood transfusion	3	0	0.0
Quinine, intravenously, and blood transfusion	2	0	0.0
Total	14	4	28.5

TABLE 7—*Incidence and Mortality Rate According to Sex in 6 Cases of Pernicious Algid Malaria*

Race	Sex	Number of Cases	Number of Deaths	Mortality Rate, Percentage
White	Male	3	1	
	Female	3	1	
Total		6	2	33.3

all cases. Since 1920, transfusions of from 200 to 500 cc of blood given once or twice daily have been used to combat hemolysis in 12 cases. In 10 patients the hemoglobinuria abated within ninety-six hours after the first transfusion, while in the other 2 coma developed and death supervened on the second day. Quinine was given after blood transfusions were begun in 5 cases, all of which terminated in recovery. Quinine administered intravenously with large amounts of dextrose solution produced no definite increase of hemoglobinuria in 2 patients who survived. The 2 patients treated only with sodium cacodylate died within thirty-six hours.

*Algid Type*—Only 6 of the cases of estivo-autumnal malaria were of the pernicious algid type. Marked but less severe abdominal symptoms were present in 3 of the patients with cerebral and in 2 of those with the hemorrhagic type of pernicious malaria. Algid malaria occurred only in white patients (table 7).

Severe headache, vomiting and abdominal pain were followed by collapse in each case of the algid type. At the time of admission, the patients with algid malaria showed prostration, profuse sweating, chilliness of the extremities and spasticity of the abdominal wall. Reduction of the systolic blood pressure was constant, and 5 patients had subnormal temperature. Dehydration was pronounced, and anemia was masked. Relatively large numbers of plasmodia were found in the blood. Coma led to death in the 2 fatal cases.

In the treatment of algid malaria, stimulants and active hydration were used as a routine. Quinine given intravenously in dextrose solution was the therapeutic measure of choice.

#### SUMMARY

Of 700 proved cases of severe malaria observed during a period of fifteen years, 198 were of the tertian and 502 of the estivo-autumnal variety. More than 70 per cent of the patients were white, although local census reports during the period showed nearly equal numbers of white and Negro residents. The mortality rate was 0.50 per cent for the tertian and 9.98 per cent for the estivo-autumnal type of malaria. Malaria was fatal primarily when it was complicated by pernicious symptoms or in the presence of advanced cardiovascular changes.

Pernicious malaria developed in 97, or 19.34 per cent, of the cases in the estivo-autumnal group, as a result of neglected or insufficient treatment. Of the pernicious cases, 74.2 per cent were in males, and 61.9 per cent in white patients. Malaria with pernicious symptoms was most frequent at the height of the season in which estivo-autumnal malaria prevails, namely, in October. Pernicious malaria was fatal in 48.4 per cent of the cases and caused 92.1 per cent of the deaths in the whole group.

Cerebral manifestations predominated in 75, or 77.3 per cent, of the cases of pernicious malaria (14.96 per cent of the estivo-autumnal group). All but 1 of the cases of pernicious malaria occurring in Negroes were of the cerebral type. Furthermore, 21 per cent of the Negro, as compared with 11.4 per cent of the white, patients with estivo-autumnal infection presented pernicious cerebral symptoms. Pernicious cerebral malaria appeared to be the usual climax of overwhelming estivo-autumnal infection, particularly in Negro patients. Coma was also present in 4 patients with the hemorrhagic, and in 2 with the algid, type of malaria, but proof that cerebral capillary embolism was present in these cases is lacking. In the cerebral type, unconsciousness was ushered in by severe headache and delirium, these symptoms were often accompanied by vomiting in adults and by convulsions in children. Plasmodia were found in the blood in numbers relatively proportional to the gravity of the cerebral symptoms. Cerebral malaria resulted in death in 50.6

per cent of the cases and was responsible for 74.5 per cent of the deaths in the whole group. The majority of the patients who survived had been in coma for less than twenty-four hours. In the treatment of cerebral malaria, quinine injected intravenously with hypertonic dextrose solution proved to be the most effective measure employed.

Pernicious hemoglobinuria occurred in 16 cases, or 3.19 per cent. of the estivo-autumnal group, only 1 of the patients being a Negro. There had been repeated malarial infection in 12 and attacks of blackwater fever in 5 of the cases. Anemia and icterus were more marked in the hemorrhagic than in the other types of pernicious malaria. In 3 cases of hemorrhagic malaria the peripheral blood showed small numbers of plasmodia. The mortality rate from hemorrhagic malaria was 37.5 per cent. On the theory that the blood of patients with blackwater fever contains an autohemolysin which may be diluted or rendered ineffective by increasing the total volume of erythrocytes, blood transfusions were employed in the treatment of 12 patients, 10 of whom survived. Although 14 patients with hemorrhagic malaria had taken medicaments containing quinine just before the onset of the disease, no increase of hemoglobinuria was noted in 5 of those who received transfusions and who were subsequently treated with quinine.

Pernicious malaria of the algid type was unusual in the whole group and was not observed in Negro patients. In 6 cases of the algid type the outstanding features were abdominal pain, vomiting followed by collapse and the presence of large numbers of parasites in the blood. The 2 patients with algid malaria who became comatose succumbed. Administration of stimulants, restoration of the fluid balance in the body and intravenous injection of quinine appeared to be the most effective therapeutic measures in pernicious cases of the algid type.

# PERSISTENT ABNORMALITIES (WASSERMANN-FASTNESS) OF THE SPINAL FLUID IN TREATED NEUROSYPHILIS

THEIR PROGNOSTIC IMPORT

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AND

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A problem of great importance in the therapy of neurosyphilis is presented by the treatment of the patient who after prolonged and intensive treatment shows persistent abnormalities in the cerebrospinal fluid. The significance of such findings is of importance to the patient and to the physician. Is a persistently positive Wassermann reaction of the spinal fluid of innocent import as is a persistently positive Wassermann reaction of the blood in well treated patients with latent syphilis, or does such Wassermann-fastness of the spinal fluid indicate that the patient is in grave danger of progression or relapse and that he must be treated for years or for a lifetime?

It is necessary to point out, of course, that in the spinal fluid, as in the blood, persistent serologic abnormalities, especially a persistently positive Wassermann reaction, may be in large part an expression of the sensitivity of the serologic tests employed. This fact has been repeatedly emphasized in the clinic at Johns Hopkins Hospital, where a sensitive Wassermann antigen with icebox incubation is employed for blood and spinal fluid alike. We have records of many patients for whom the Wassermann reaction of the spinal fluid was reversed to negative by a less delicate technic carried out in our own or in another laboratory but was found to be strongly and persistently positive when the sensitivity of the test was increased.

It seemed to us that the significance of Wassermann-fastness of the spinal fluid could be determined only by the clinical approach that one of us (J E M) made to the problem of Wassermann fastness of the blood,<sup>1</sup> namely: Is the probability of clinical progression or relapse

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1 Moore, J E. Wassermann Fast Patients, in Blumer, George. The Practitioner's Library of Medicine and Surgery, New York, D Appleton-Century Company, Inc., 1934, vol 13, chap 18

greater in a series of Wassermann-fast patients followed over a long period of time than in an equal series of patients with clinically similar manifestations in whom reversal of the reaction has been secured by treatment?

A preliminary study of this question has already been attempted in a study of 46 well treated neurosyphilitic patients with a persistently positive reaction of the spinal fluid<sup>2</sup> Of these, 35 (76 per cent) were free from relapse or progression of syphilis of the nervous system at intervals ranging from two to twenty years after the cessation of treatment From this small series it was concluded

with various forms of central nervous system syphilis persistently positive spinal fluid abnormalities do not indicate the certainty of subsequent progression or relapse, provided the patient has been subjected to intensive, prolonged and continuous treatment for a minimum period of from two to three years, provided this treatment has brought about symptomatic improvement, and especially provided malaria has been included in the treatment plan

It was appreciated that the group of patients studied was relatively small In this present study we have reviewed the cases of a larger series of patients with a persistently positive reaction of the spinal fluid<sup>3</sup> and have compared the clinical outcome in these patients with that in a parallel group of patients for whom the reaction of the spinal fluid had been "reversed" to normal by treatment

Two hundred and twelve patients were selected from those seen at the division for syphilitic patients of the medical clinic of the Johns Hopkins Hospital and from patients observed in private practice Patients were included only (1) if they had received prolonged treatment, resulting in marked improvement or complete relief from symptoms and (2) if after the conclusion of treatment the course of the disease had been ascertained by repeated neurologic and serologic examinations for at least two years

Of the 212 patients qualified for study in this fashion, 95 showed a persistently positive Wassermann reaction of the spinal fluid, for 117 the reaction of the fluid was reversed by treatment

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2 Moore, J E The Modern Treatment of Syphilis, Springfield, Ill, Charles C Thomas, Publisher, 1933, p 412

3 We have thought it wise, for the purpose of this study, to limit the terms "persistently abnormal spinal fluid" and "fluid giving a persistently positive reaction" to fluids which gave a positive Wassermann reaction with some amount of fluid in spite of treatment Thus, a patient for whom the Wassermann reaction of the spinal fluid was positive at the start of treatment with 0.05 cc and at the end of treatment only with 1 cc is classified as Wassermann-fast, even though marked improvement has occurred With the small amount of material available we have been unable to study the influence on the clinical outcome of such factors as persistent slight pleocytosis, excess of protein or changes in the colloidal gold curve



The incidence of clinical progression in the patients with a persistently positive Wassermann reaction of the spinal fluid and in those in whom the reaction was reversed by treatment is shown comparatively in table 1. By the term clinical progression or relapse we refer here only to advance of the disease of the central nervous system. Some patients suffered from associated cardiovascular or visceral syphilis, and in several instances such lesions led to death. Two instances of cerebral vascular accidents included in this study are recorded as evidence of progressive neurosyphilis, though the cause of the lesion may well have been hypertension. Of the 95 patients who showed a persistently posi-

TABLE 1—*Relationship of Clinical Progression of Neurosyphilis to Effect of Treatment on Spinal Fluid in 212 Cases*

Cerebrospinal Fluid Outcome	Result of Treatment	Patients		Period of Observation After Treatment			
		Total Number	Per Cent	2 5 Years	6 10 Years	11 15 Years	16 Years
Persistently positive reaction (95 patients)	Clinical progression	21	22.1	17	4		
	No progression	74	77.9	37	30	6	1
Reversal of reaction after treatment (117 patients)	Clinical progression	8	6.8	4	3	1	
	No progression	109	93.2	67	41	1	

TABLE 2—*Relationship of Amount of Treatment to Clinical Progression in Wassermann-Fast Patients and Patients with Reversed Reactions*

Cerebrospinal Fluid	Duration of Treatment	Number of Patients	Clinical Progression	
			Number of Patients	Per Cent
Persistently positive reaction (95 patients)	6 mos. to 2 yrs	31	13	41.9
	Over 2 yrs	64	8	12.5
Reversal of reaction after treatment (117 patients)	6 mos. to 2 yrs	34	4	11.7
	Over 2 yrs	83	4	4.8

tive Wassermann reaction of the spinal fluid after treatment, 21 (22.1 per cent) showed some evidence of clinical progression after the cessation of treatment. Of the 117 in whom the Wassermann reaction of the spinal fluid was reversed to negative only 8 (6.8 per cent) subsequently showed evidence of clinical advance of neurosyphilis.

In table 2 the patients are further classified according to the total amount of treatment which they received. In the group who received treatment for two years or more, the incidence of relapse or progression was 12.5 per cent in the Wassermann-fast patients, but only 4.8 per cent in the patients who showed reversal of the reaction of the spinal fluid. In the group who received treatment for from six months to two years relapse occurred in 41.9 per cent of the Wassermann-fast patients and in only 11.7 per cent of the patients with reversal of the

reaction of the spinal fluid In both groups the incidence of progression was considerably lower than we anticipated These data are subject to further modification on the ground that the patients have been followed for an average period of only five and a half years from the time of cessation of treatment It is probable that as the period of observation is prolonged the incidence of relapse will increase, though in the majority of instances of progression so far observed renewed activity of the neurologic lesion has occurred within five years after the cessation of treatment

In table 3, the patients are grouped according to the type of neurosyphilis, and the appearance of clinical progression or relapse is contrasted in patients with parenchymatous and in those with nonparenchymatous forms of the disease It is not surprising that the majority

TABLE 3—*Relationship of Clinical Progress to Type of Neurosyphilis*

Type of Neurosyphilis	Persistently Positive Reaction of Cerebrospinal Fluid				Reversal of Reaction of Cerebrospinal Fluid			
	Total Number of Patients	Number Showing Clinical Progress	Percent age	Average Period of Observation After Treatment	Total Number of Patients	Number Showing Clinical Progress	Percent age	Average Period of Observation After Treatment
Dementia paralytica and tabes (paren- chymatous neuro- syphilis)	42	14	33.3	5.3 yrs	31	6	19.3	6.2 yrs
Meningovascular, vascular, meningeal and asymptomatic (nonparenchyma- tous neurosyphilis)	53	7	13.2	6.0 yrs	86	2	2.3	5.2 yrs

of instances of clinical progression occurred in patients with tabes and dementia paralytica Though this group comprised only 34 per cent of the patients, it presented 69.2 per cent of those in whom relapse occurred In the group with the parenchymatous form of the disease progression occurred in 33.3 per cent of the Wassermann-fast patients and in only 19.3 per cent of those in whom the reaction of the spinal fluid became negative In the group with meningovascular, vascular, meningeal or asymptomatic (presumably "nonparenchymatous") neurosyphilis relapse was six times as common in the Wassermann-fast patients as in those for whom the reaction of the spinal fluid became negative The total incidence of progression in this group is surprisingly low Such clinical relapse occurred in only 1 of 7 Wassermann-fast patients and in only 1 of 43 patients in whom a reversal of the reaction occurred

The type of clinical progress in the various types of neurosyphilis is illustrated in table 4 It will be noted that 5 of 9 relapses occurring

in the patients with nonparenchymatous neurosyphilis took the form of dementia paralytica. Of the 10 patients with dementia paralytica who subsequently had a relapse, 6 showed progressive mental deterioration. The cases of 2 of the patients with tabes who had a relapse illustrated the curious phenomenon which we have observed a number of times the development of Charcot joints in the face of complete reversal of the reaction of the spinal fluid. It is noteworthy that not one of the patients with dementia paralytica in whom reversal of the reaction

TABLE 4—*Nature of Relapse or Progression in 212 Patients with Neurosyphilis\**

Type of Neurosyphilis	Persistently Positive Reaction of Cerebrospinal Fluid			Reversal of Reaction of Cerebrospinal Fluid		
	No of Patients	No of Patients with Relapses	Type of Relapse or Progression	No of Patients	No of Patients with Relapses	Type of Relapse or Progression
Dementia paralytica	26 (14)	10 (1)	6 (1) relapse or progression of dementia paralytica 1 cerebral hemorrhage (? syphilitic) 1 formication of the face 1 hemiplegia 1 optic atrophy	11 (6)	0	
Tabes	16 (2)	4 (0)	1 locomotor ataxia worse 1 general progression 1 gastric crises worse 1 vesical symptoms worse	20 (3)	6 (1)	1 bilateral Charcot hip 1 ataxia worse 1 Charcot knee 2 (1) increased lightning pains 1 Charcot joint worse
Diffuse meningo-vascular	28 (4)	2 (0)	1 involvement of eighth nerve 1 dementia paralytica	28 (1)	1	1 Parkinson syndrome (? syphilitic)
Meningeal	9	2	2 dementia paralytica	25	1	1 optic atrophy
Asymptomatic	16 (2)	3 (0)	2 dementia paralytica 1 hemiplegia (? syphilitic)	33 (2)	0	
	95	21		117	8	

\* The figures in parentheses indicate the number of patients who received fever therapy

occurred had a relapse in an average period of five and one-tenth years following treatment

Of the 212 patients in this series, 31 received fever therapy (malaria, 29, typhoid vaccine, 1, rat-bite fever, 1) at one time or another in the course of treatment. Of the 22 of these patients who had tabes or dementia paralytica, progression occurred in only 2. Of the 9 patients with nonparenchymatous neurosyphilis who received fever therapy, progression occurred in none.

Table 5 is analogous to table 3, except that in it the data on the patients who received fever therapy have been omitted. Table 5 records the incidence of clinical relapse in patients treated for more than six

months with chemotherapy alone (85 per cent received treatment for more than one year, 65 per cent, for more than two years) In this table is illustrated a striking association between the clinical outcome and the effect of treatment on the spinal fluid Fifty per cent of the patients with tabes and dementia paralytica who showed a persistently positive reaction of the spinal fluid and only 20 per cent of those in the group in which the reaction of the spinal fluid became negative had a relapse In the group with nonparenchymatous forms, 17 per

TABLE 5—*Incidence of Relapse in Patients for Whom Chemotherapy Alone Was Used*

	Persistently Positive Reaction of Cerebrospinal Fluid			Reversal of Reaction of Cerebrospinal Fluid		
	No of Patients	No of Patients with Relapses	Percentage of Relapses	No of Patients	No of Patients with Relapses	Percentage of Relapses
Dementia paralytica, tabes	26	13	50.0	25	5	20.0
Vascular, meningovascular, asymptomatic	47	7	17.0	83	2	2.4
Total	73	20	27.4	108	7	6.4

TABLE 6—*Incidence of Relapse in Patients Receiving Chemotherapy for Two Years or More and No Fever*

	Persistently Positive Reaction of Cerebrospinal Fluid			Reversal of Reaction of Cerebrospinal Fluid		
	No of Patients	No of Patients with Relapses	Percentage of Relapses	No of Patients	No of Patients with Relapses	Percentage of Relapses
Dementia paralytica, tabes	13	3	23.0	17	4 (all tabetic)	23.5
Vascular, meningovascular, asymptomatic	28	3	10.7	50	0	0
Total	41	6	14.6	67	4	5.9

cent of the Wassermann-fast patients and only 2 per cent of those with a reversed reaction had a relapse If we further limit the patients to those treated only with chemotherapy for a period of two years or more, we find that 14.6 per cent of the Wassermann-fast patients showed progression as compared with 5.9 per cent of those for whom the reaction was reversed to negative by treatment

#### COMMENT

It appears from the data presented here that in neurosyphilis there is a definite relationship between the response of the reaction of the cerebrospinal fluid to treatment and the probability of subsequent clin-

ical progression or relapse Among the 181 patients treated only with chemotherapy, relapse occurred four times as often in patients who had persistently positive reactions of the spinal fluid as in those whose reactions were reversed to negative by treatment The relatively benign character of the nonparenchymatous types of neurosyphilis is emphasized throughout this study In the cases in which the condition was classified as meningeal, meningovascular, vascular or asymptomatic neurosyphilis, clinical progression occurred in only 10.7 per cent of the Wassermann-fast patients and in none of 50 patients for whom the reaction of the fluid was reversed to negative In only 2 (6.4 per cent) of the 31 patients who received fever therapy in the course of their treatment did the condition progress in an average period of five and one-half years after the cessation of treatment, in both of these instances the reaction of the spinal fluid was persistently positive

The relationship of the amount of treatment to the incidence of clinical relapse is apparent from this study Subsequent progression occurred from two to three times more commonly in patients who received treatment for from one-half to two years than in those who received treatment for two years or more

Reversal of the reaction of the spinal fluid by treatment seems to carry different omens, depending on the clinical type of neurosyphilis In tabes, for instance, a return of the spinal fluid to normal following treatment indicates nothing prognostically, because relapse is just as likely to occur as if the reaction of the fluid remained positive In dementia paralytica, however, a reversal of the reaction was associated with no instances of clinical progression Likewise, in vascular, meningovascular, meningeal or asymptomatic neurosyphilis, a reversal of the reaction was an exceedingly favorable sign

However, although the persistently positive reaction of the spinal fluid in neurosyphilis is definitely of graver prognostic import than the persistently positive Wassermann reaction of the blood in such conditions as latent, benign late, and late congenital syphilis, it does not signify the inevitability of subsequent progression or of relapse, and like Wassermann-fastness of the blood it cannot be used as a guide to the optimum duration of treatment Considering neurosyphilitic patients as a group, without differentiation according to the clinical type of the disease presented, it appears that when treatment is continued for a minimum period of two years, and especially if at some time malaria is included in the treatment, subsequent progression within a five year period of observation occurs in only 1 patient of every 8 (12.5 per cent), even though a positive reaction of the spinal fluid persists Such well treated patients may therefore be given encouraging reassurance as to the probability of continued good health

As for the optimum duration of treatment for patients with neurosyphilis, no hard and fast rules can be laid down. In general, it may be stated that the duration of treatment should depend more on clinical improvement and lack of progression than on reversal of the serologic reaction and that for no type of neurosyphilis should the total duration of treatment be less than two years of continuous treatment or its equivalent. In the case of patients for whom the reaction of the spinal fluid remains persistently positive after this amount of chemotherapy every effort should be made to utilize the beneficial prophylactic effect of fever therapy (malaria) before treatment is finally discontinued.

#### SUMMARY

We present a study of the incidence of clinical progression or relapse after prolonged treatment in 212 patients with neurosyphilis.

A comparison is made between two groups: 95 patients for whom the reaction of the spinal fluid which remained persistently positive and 117 for whom the positive reaction was reversed by treatment.

Considering the groups as a whole, clinical progression occurred in 22 per cent of the Wassermann-fast patients and in only 7 per cent of those with reversed reactions.

Limiting the study to patients treated for two or more years, subsequent progression occurred in 12.5 per cent of the Wassermann-fast group and in 4.8 per cent of the group with reversed reactions.

Progression or relapse is more common in patients with parenchymatous neurosyphilis (tabes and dementia paralytica) than in those with nonparenchymatous types of neuaxis involvement.

Even in a patient with apparently nonparenchymatous neurosyphilis, the subsequent relapse, if one occurs, is likely to be dementia paralytica in type.

Of 31 patients in this series treated at some time with induced fever therapy (chiefly malaria), subsequent progression or relapse occurred in only 2.

While there is a more definite relationship between the clinical outcome and the reaction of the spinal fluid in neurosyphilis than between the reversal or the fastness of the Wassermann reaction of the blood in various forms of late syphilis not involving the nervous system, a persistently positive reaction of the spinal fluid does not indicate the inevitability of subsequent progression or of relapse, nor can the rate or completeness of reversal of the reaction be used as the sole guide to the optimum duration of treatment in cases of neurosyphilis.

# FAT ABSORPTION

ITS VALUE AS AN INDEX OF FUNCTION OF THE LIVER

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AND

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NEW ORLEANS

Using the Ruckert volumetric lipokrit method,<sup>1</sup> we have determined the total serum lipoids of a group of normal young men, a group of diabetic patients, and a group of patients with disease of the liver, first in the fasting state and then three, six and nine hours after a fat meal. This was done to determine whether or not we could obtain curves showing fat absorption which would be typical for each group and sufficiently characteristic in the cases of the normal subjects and patients with disease of the liver to aid in the appraisal of the function of the liver.

## NORMAL ABSORPTION VALUES

The group of normal young men was comprised of forty-three medical students, ranging in age from 21 to 29, with an average age of 24.1. After a fast of fifteen hours, blood was taken by venipuncture. Immediately afterward, each student drank 100 Gm (120 cc) of cottonseed oil, which was from 1 to 1.8 Gm of fat per kilogram of body weight. Three, six and nine hours later samples of blood were obtained by venipuncture and the values of the total serum lipoid were determined. No attempt was made to calculate the relative amounts of neutral fat and cholesterol and of phosphatide making up the total. The final step of converting the fatty acid fraction to phosphatide was omitted, and the total lipoids were expressed in cc per hundred cubic centimeters. The total amounts of carbohydrate, protein and fat consumed during the twenty-four hours preceding the test were calculated. The amount of food that each student ate on this day represented as nearly as possible his average daily consumption.

The results of the determinations of the total serum lipoid, the average daily diets and the body weights are recorded in table 1. After fasting the average value for the forty-three men was 0.576 cc per

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1 Ruckert, W. Eine einfache volumetrische Mikrobestimmung des Blutfettes (Lipokritverfahren), *Klin Wchnschr* **10** 1853 (Oct 3) 1931

TABLE 1—Total Blood Serum Lipoids of Normal Young Men Before and After the Ingestion of One Hundred Grams of Cottonseed Oil, Also the Amounts of Carbohydrate, Protein and Fat Consumed the Day Before the Test \*

Case	Lipoids				Carbohy- drates, Gm	Protein, Gm	Fat, Gm	Total Calories	Weight, Kg	Calories per Kg
	Fasting	After 3 Hours	After 6 Hours	After 9 Hours						
1	0.52	0.600 (+15.1%)	0.110 (+111%)	0.550 (+5.7%)	300.1	92.6	128.8	2,801.3	62.8	44.6
2	0.48	0.680 (+46.2%)	0.600 (+25%)	0.520 (+8.3%)	323.4	123.4	173.7	2,222.3	63.0	35.2
3	0.40	0.560 (+40%)	0.800 (+100%)	0.450 (+2%)	234.0	90.0	75.0	2,161.0	63.0	34.1
4	0.52	0.800 (+53.8%)	0.640 (+22.2%)	0.640 (+22.2%)	330.6	103.9	149.3	3,106.8	59.0	38.8
5	0.52	0.840 (+61.5%)	0.120 (+13.0%)	0.630 (+30.7%)	330.6	103.9	149.3	3,106.8	73.6	42.0
6	0.40	0.440 (+10%)	0.124 (+20.0%)	0.440 (+10%)	214.6	98.1	253.9	3,539.0	71.8	49.9
7	0.52	0.560 (+7.5%)	0.130 (+18.0%)	0.800 (+53.8%)	299.0	90.5	115.4	2,726.5	73.0	36.3
8	0.60	0.760 (+26.6%)	0.100 (+6.6%)	0.720 (+20%)	341.5	97.5	151.6	2,900.9	41.1	11.6
9	0.52	0.680 (+34.6%)	0.600 (+15.4%)	0.450 (-7.6%)	338.8	85.8	179.9	3,356.6	73.0	11.6
10	0.60	0.880 (+46.6%)	0.660 (+10%)	0.600 (+0%)	230.0	220.0	110.0	2,790.0	76.3	36.5
11	0.80	0.880 (+10%)	0.104 (+30.7%)	0.720 (-10%)	230.9	87.8	117.0	2,549.4	72.7	35.0
12	0.80	0.960 (+20%)	0.116 (+45.7%)	0.720 (-10%)	324.5	101.4	106.2	2,674.0	83.0	31.4
13	0.72	0.880 (+22.5%)	0.100 (+38.7%)	0.760 (+5.5%)	314.2	83.6	113.4	2,663.0	80.0	33.2
14	0.64	0.740 (+15.6%)	0.580 (-9.3%)	0.560 (-12.6%)	263.4	130.4	152.2	3,284.7	78.0	56.6
15	0.80	0.960 (+20%)	0.104 (+30.7%)	0.840 (+2%)	273.5	113.9	138.6	2,914.5	69.1	42.7
16	0.72	0.104 (+4.4%)	0.800 (+11.1%)	0.760 (+5.2%)	202.4	86.0	89.1	1,933.1	64.5	29.9
17	0.60	0.760 (+26.6%)	0.700 (+16.6%)	0.660 (+10%)	291.0	116.0	145.0	2,913.0	74.0	39.3
18	0.40	0.440 (+10%)	0.590 (+15.8%)	0.400 (+0%)	246.1	92.4	115.8	2,329.5	53.4	44.5
19	0.68	0.920 (+35.2%)	0.880 (+29.4%)	0.680 (+0%)	306.5	141.0	170.8	3,315.0	84.1	41.8
20	0.60	0.840 (+33.3%)	0.800 (+33.3%)	0.740 (+1%)	378.3	118.7	143.3	3,238.0	79.3	40.9
21	0.96	0.112 (+1.6%)	0.104 (+8.3%)	0.930 (+)	234.9	91.6	131.3	2,444.2	100.0	21.4
22	0.46	0.540 (+17.3%)	0.500 (+8.6%)	0.420 (-)	264.3	105.0	89.9	2,269.8	82.0	27.6
23	0.54	0.600 (+11%)	0.680 (+27.7%)	0.440 (-)	309.0	82.0	99.2	2,277.8	77.2	30.7
24	0.64	0.840 (+31.2%)	0.680 (+5.8%)	0.640 (-)	399.5	154.6	92.5	2,919.5	62.0	47.0
25	0.48	0.800 (+66.6%)	0.680 (+45.8%)	0.480 (+)	261.0	72.8	132.1	2,833.2	63.3	35.3
26	0.52	0.720 (+38.4%)	0.720 (+38.4%)	0.520 (+)	207.4	97.3	133.5	2,373.7	78.6	29.5
27	0.48	0.600 (+25.4%)	0.880 (+83.8%)	0.440 (-)	336.5	86.9	118.9	2,820.0	62.7	36.8
28	0.56	0.700 (+26.7%)	0.680 (+21.4%)	0.580 (+)	215.5	106.5	131.1	2,806.7	80.0	33.0
29	0.50	0.600 (+7.1%)	0.720 (+28.3%)	0.580 (+)	342.7	129.7	132.7	2,814.9	58.1	18.4
30	0.64	0.800 (+25.3%)	0.760 (+18.7%)	0.680 (+)	310.0	117.7	118.3	2,755.4	74.0	37.7
31	0.53	0.740 (+27.5%)	0.800 (+36.2%)	0.520 (-)	234.5	90.8	75.7	2,345.3	72.7	32.2
32	0.50	0.680 (+36.9%)	0.500 (+0%)	0.460 (-8%)	141.7	64.9	75.8	1,508.6	65.9	22.8
33	0.52	0.740 (+42.3%)	0.600 (+13.5%)	0.580 (+11.5%)	285.0	90.0	75.0	2,175.0	77.0	26.0
34	0.56	0.760 (+37.5%)	0.840 (+50%)	0.640 (+14.2%)	323.6	86.6	175.7	2,697.0	59.9	45.0
35	0.60	0.720 (+20%)	0.620 (+3.5%)	0.600 (+0%)	298.4	93.4	162.2	2,940.7	67.2	43.7
36	0.64	0.760 (+18.7%)	0.720 (+12.6%)	0.640 (+0%)	303.6	116.2	150.2	3,147.2	78.0	40.3
37	0.56	0.800 (+42.8%)	0.800 (+42.8%)	0.560 (+0%)	323.1	120.9	132.0	2,981.4	75.0	39.7
38	0.52	0.920 (+76.9%)	0.720 (+38.4%)	0.680 (+32.3%)	321.0	103.0	141.0	2,935.0	69.0	40.3
39	0.56	0.720 (+28.5%)	0.112 (+100%)	0.880 (+57.1%)	238.9	72.0	87.3	2,101.5	61.3	31.1
40	0.68	0.760 (+11.7%)	0.760 (+11.7%)	0.560 (-21.4%)	310.4	98.1	97.7	2,519.0	64.0	39.2
41	0.64	0.890 (+37.5%)	0.920 (+43.7%)	0.640 (+0%)	231.4	104.7	110.3	2,096.5	65.9	36.8
42	0.56	0.800 (+42.8%)	0.760 (+35.9%)	0.560 (+0%)	263.3	76.5	48.3	1,687.1	76.8	21.9
43	0.42	0.520 (+23.8%)	0.560 (+33.8%)	0.400 (-4.7%)	298.8	100.6	91.2	2,385.5	67.7	35.2
Average	0.576	+30.1%	+65.4%	+5.1%						

\* The values for carbohydrates, protein and fat represent the average daily intake. In all the tables the values for blood serum lipoids are given in cubic centimeters per cent.



hundred cubic centimeters. The only other published figures of serum lipoids of normal men determined by this method are those of Collins.<sup>2</sup> However, his data should not be compared strictly with ours. His samples of blood were taken at 11 a. m. after a fast of only three hours. The amount of food eaten at each breakfast was not known and it is quite likely that the fat contents varied considerably. On the other hand, all of our subjects had fasted for from fifteen to sixteen hours, and there was no question of the influence of absorption. Collins' figures, however, are remarkably similar to ours. His average value for thirty-eight normal men was 0.566 cc per hundred cubic centimeters. Boyd,<sup>3</sup> using a micro-oxidative method, determined the total serum fats of eight normal, nonpregnant, nonmenstruating young women in the fasting state. The mean value that she obtained was 589 mg per hundred cubic centimeters. Our data show (table 1) that the effect of body weight apparently has no relation to the total serum lipoids in the fasting state, nor do high, moderate or low fat diets seem to influence the level of serum fats. Among these determinations on normal subjects in the fasting state there was only one (case 21) in which the value appeared to be abnormally high 0.96 cc per hundred cubic centimeters. This determination was repeated several days later and the result was the same. The subject was an obese young Jew in whose family there were many cases of diabetes and much obesity. After a fast his blood sugar level, although normal, was in the upper limit of normal 0.12 Gm per hundred cubic centimeters. He could, therefore, be classified as a potential diabetic or prediabetic patient. Collins<sup>2</sup> determined the total serum lipoids of 103 diabetic patients. The average mean serum fat he found to be 0.818 cc per hundred cubic centimeters. He concluded that "a serum fat concentration exceeding 0.82 cc per cent may be considered as strong evidence that the case is one of diabetes."

There are no data concerning alimentary lipemia and blood fat values following the ingestion of fat which are properly comparable to these data. Numerous studies<sup>4</sup> have been made in the attempt to eluci-

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2 Collins, D. H. Diabetic Lipaemia, The Rôle of the Fats in Diabetes Mellitus, with a Description of the Haemolipokrit Method for the Estimation of Fat in the Blood-Serum, *Quart J Med* **2** 267 (April) 1933.

3 Boyd, E. M. A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, *J Biol Chem* **101** 323 (June) 1933.

4 (a) Burger, M., and Habs, H. Ueber Störungen der Cholesterin- und Fettresorption bei Lebercirrhose, *Klin Wchnschr* **6** 2125 (Nov 5) 1927. (b) Man, E. B., and Gildea, E. F. The Effect of the Ingestion of a Large Amount of Fat and of a Balanced Meal on the Blood Lipids of Normal Man, *J Biol Chem* **99** 61 (Dec) 1932. (c) Bang, I. Ueber Lipämie, *Biochem Ztschr* **91** 104, 1918. (d) Cowie, D. M., and Hoag, L. A. Studies in Blood Fat, *J A M A* **77** 1493 (Nov 5) 1921. (e) Hiller, A., Linder, G. C., Lundsgaard, C., and Van Slyke, D. D.

date the question of fat absorption and to determine whether there is a fat absorption curve which conforms to a uniform pattern, but there has been much disagreement in the results of these investigations and concerning the question of the utilization of fat in general. This is due in part to the complexity of the subject and in part to the fact that various methods for determining lipid values, some of which have been adversely criticized, have been employed and in many instances different fractions instead of total lipoids have been studied. Determinations were made in some studies on whole blood and in others on plasma, and the fat meal has not been the same in all of the investigations. The uniformity of our curves is striking for they correspond to a definite pattern. The average rise at three hours was +30 per cent and at six hours, +65 per cent. In nine hours the level had fallen practically to the level for the fasting state +5 per cent. Thus a typical curve could be plotted showing that the height of absorption

TABLE 2—*Total Blood Serum Lipoids in Ten Diabetic Patients Before and After the Ingestion of One Hundred Grams of Cottonseed Oil*

Case	Fasting	After 3 Hours	After 6 Hours	After 9 Hours
1	0.68	0.800 (+17.9%)	0.132 (+94.1%)	0.980 (+44.2%)
2	0.32	0.560 (+75%)	0.720 (+156.2%)	0.640 (+100%)
3	0.60	0.800 (+33.3%)	0.104 (+73.3%)	0.920 (+53.3%)
4	0.70	0.900 (+28.5%)	0.104 (+48.5%)	0.920 (+31.4%)
5	0.84	0.104 (+23.8%)	0.104 (+23.8%)	0.110 (+30.9%)
6	0.84	0.860 (+2.3%)	0.920 (+9.5%)	0.800 (-4.7%)
7	0.60	0.680 (+13.3%)	0.760 (+26.6%)	0.720 (+20%)
8	0.80	0.100 (+25%)	0.128 (+60%)	0.132 (+65%)
9	0.66	0.880 (+33.3%)	0.960 (+45.4%)	0.960 (+45.4%)
10	0.44	0.680 (+54.5%)	0.960 (+118.1%)	0.600 (+36.3%)

most likely was reached somewhere between the third and the sixth postprandial hour and that between the sixth and the ninth postprandial hour, probably about the seventh, absorption had ceased.

#### ABSORPTION CURVES IN DIABETES

In table 2 are recorded the absorption curves of ten clinically well stabilized diabetic patients. These curves differed from those of normal subjects in a manner that might have been expected. The average rise at the third and sixth postprandial hours was +27.2 per cent and +60 per cent, practically the same as that of normal persons, but at the ninth postprandial hour the lipid level was still elevated +42.1 per cent.

Fat Metabolism in Nephritis, J. Exper. Med. **39** 931 (June) 1924. (f) McClure, C. W., and Huntsinger, M. E. Studies in Fat Metabolism, Influence on Blood Lipids of Single Foodstuffs, J. Biol. Chem. **76** 1 (Jan.) 1928. (g) Page, I. H., Pasternack, L., and Burt, M. L. Ueber den Transport von Fetten und Lipoiden durch Blut nach Oeleingabe, Biochem. Ztschr. **223**.445, 1930. (h) Wechsler, H. F., Variations in Total Blood Lipid in Alimentary Lipemia, Arch. Int. Med. **50** 37 (July) 1932.

Although the question of the utilization of fat has never been satisfactorily elucidated, there is considerable evidence that such utilization requires a normally functioning liver<sup>5</sup> Therefore, patients with evidence of disease of the liver should show a diminished and delayed ability to absorb fats It is obvious, of course, that there must be numerous other factors which would contribute to a delayed rate of absorption, such as disease of the lining of the gastro-intestinal tract, increased mobility of the tract, absence of enzymes, interference with the production of bile and surgical excision of parts of the gastro-intestinal tract Any of these conditions may be present in persons with disease of the liver Frequently, gastritis complicates and, indeed, is even considered a part of cirrhosis of the liver Thus, although delayed absorption of ingested fat will occur when there is diminished function of the liver, the other conditions mentioned will probably result in the same type of curve Because of this the test is more useful for its negative value When a normal type of absorption curve is obtained it seems reasonable to conclude that there is no extensive damage of the liver

#### ABSORPTION CURVES IN DISEASE OF THE LIVER

In table 3 are shown the absorption curves of ten patients with definite evidence of disease of the liver These curves also conform to a special pattern The average rise at the third, sixth and ninth post-prandial hours was +89, +169 and +226 per cent, respectively The absorption was both diminished and delayed Except in case 7, in which cirrhosis was of mild degree, the level at the ninth hour was always the highest, which indicated that absorption was not yet complete In cases 3 and 5 the tests were repeated after two months, and similar curves were obtained A practical application of the test is illustrated in cases 9 and 10 Case 9 was that of a pregnant woman, aged 20, with congenital syphilis, who had been treated inadequately at 12 A course of injections of a bismuth preparation was started preparatory to the administration of arsphenamine The sixth injection was followed by epigastric pain and jaundice which lasted for two weeks

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5 (a) Burger and Habs<sup>4a</sup> (b) Leathes, J B, and Raper, H S The Fats, ed 2, New York, Longmans, Green & Company, 1925 (c) London, E S *Ergebn d Physiol* **26** 320, 1928, quoted by Bloor, W R Fat Metabolism, in Luck, J M Annual Review of Biochemistry, Stanford University, Calif, Stanford University Press, 1933, vol 3, p 185 (d) Artom, C *Arch d fisiol* **32** 57, 1933, quoted by Bloor, W R Fat Metabolism, in Luck, J M Annual Review of Biochemistry, Stanford University, Calif, Stanford University Press, 1933, vol 3, p 185 (e) Gardner, J A, and Gainsborough, H Blood Cholesterol Studies in Biliary and Hepatic Disease, *Quart J Med* **23** 465 (July) 1930 (f) Epstein, E Z Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, *Arch Int Med* **50** 203 (Aug) 1932

The liver was found to be enlarged. The fat absorption curve was of the cirrhotic type and, although it was highly desirable to treat the patient with arsphenamine, this was withheld because of the fear of a hepatotoxic effect. Had we obtained a normal type of curve we should not have hesitated to give arsphenamine. Case 10 was that of a young man who had received injections of neoarsphenamine two years before during the early stage of syphilis. After the fourth injection arsenical dermatitis and hepatitis had developed. In the interim he had been given many

TABLE 3—*Total Blood Serum Lipoids in Ten Patients with Disease of the Liver Before and After the Ingestion of One Hundred Grams of Cottonseed Oil*

Case	Fasting	After 3 Hours	After 6 Hours	After 9 Hours	
1	0.48	0.64 (+33.3%)	0.68 (+41.6%)	0.72 (+50%)	Patient with enlarged liver and palpable spleen, high icterus index, recent jaundice
2	0.48	0.48	0.56 (+16.6%)	0.56 (+16.6%)	Classic type of cirrhosis of liver
3	0.64	0.64	0.68 (+6.2%)	0.72 (+10.9%)	Arteriosclerotic heart disease with enlarged heart and congestive failure, liver enlarged
	0.34	0.36 (+5.8%)	0.40 (+11.1%)	0.40 (+11.1%)	At autopsy enlargement was found to be due to congestion and fibrosis, the second curve was determined two months later and on the day of death
4	0.80	0.80	0.84 (+5%)	0.92 (+15%)	Cirrhosis of liver and chronic gastritis
5	0.60	0.68 (+13.3%)	0.72 (+20%)	0.72 (+20%)	Syphilitic cirrhosis of liver with spleno- megaly, syphilitic heart disease, the second curve was determined two months later
	0.60	0.72	0.80	0.92	
6	0.72	0.88 (+23.5%)	0.88 (+23.5%)	0.88 (+23.5%)	Cirrhosis of liver (alcoholic)
7	0.64	0.72 (+12.5%)	0.80 (+25%)	0.72 (+12.5%)	Generalized arteriosclerosis, mild cirrhosis of liver
8	0.48	0.52 (+8.3%)	0.60 (+25%)	0.66 (+37.5%)	Cirrhosis of liver
9	0.68	0.68	0.72 (+5.5%)	0.76 (+10.2%)	Pregnant young woman with congenital syphilis in whom jaundice and epigastric pain developed during syphilitic treatment, liver palpable
10	0.48	0.48	0.52 (+3.3%)	0.64 (+33.3%)	Young man in whom arsenical dermatitis and hepatitis had developed two years pre- viously following injections of neoarsphen- amine during early stage of syphilis, liver was markedly enlarged and achylia was present

injections of a bismuth preparation and a great deal of mercury. His liver, formerly greatly enlarged, had decreased considerably in size and he felt fairly well at the time of the present investigation. The typical cirrhotic type of fat absorption curve which was obtained in this case demonstrated that any resumption of the arsenicals was perhaps forever contraindicated.

#### SUMMARY

The average value of total serum lipoids in the fasting state, determined by the Ruckert volumetric lipokrit method, for forty-three healthy young men was 0.576 cc per hundred cubic centimeters. Body weight

and diet apparently had no effect on the level of the total lipoids during fasting. The only member of this group who had what appeared to be an abnormally high serum lipoid value was an obese young Jew who was in a prediabetic state. Fat absorption curves following the ingestion of 100 Gm of cottonseed oil were determined for a group of normal young men, a group of diabetic patients and a group of patients with disease of the liver. For each group a typical curve conforming to a uniform pattern was plotted (chart). In the normal group the average rise at three hours was +30 per cent and at six hours, +65 per cent. In nine hours the lipoids had fallen practically to the level for the fasting state,

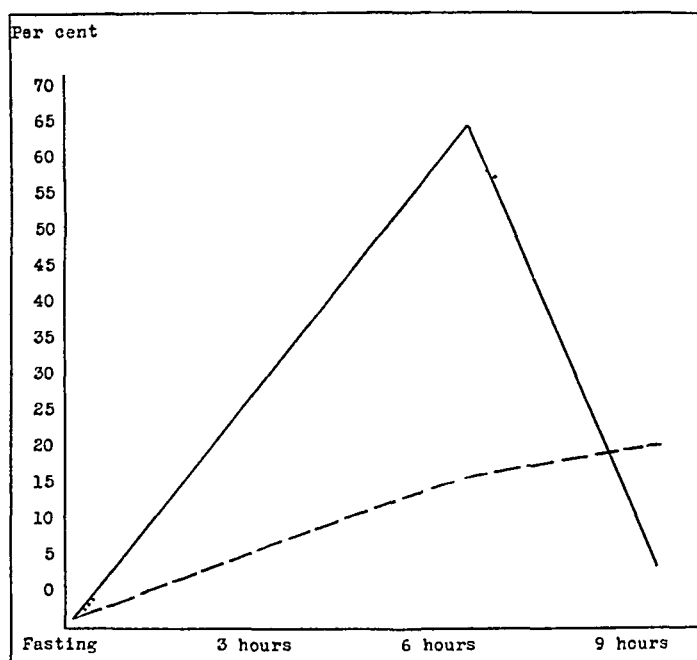


Chart showing percentage of fat absorption after the ingestion of 100 Gm (120 cc) of cottonseed oil. The unbroken line is the curve for the group of normal young men, the dotted line, for the diabetic patients, and the dash line, for the patients with disease of the liver. The normal curve equals +30 per cent at three hours, +65 per cent at six hours and +5.1 per cent at nine hours. The curve in diabetes equals +27.2 per cent at three hours, +60 per cent at six hours and +42.1 per cent at nine hours. The curve in disease of the liver equals +8.9 per cent at three hours, +16.9 per cent at six hours and +22.6 per cent at nine hours.

+5 per cent. The height of absorption probably occurred some time between the third and the sixth postprandial hour, and shortly after the sixth hour the absorption ceased. For the third and sixth hours the curves for the diabetic patients closely resembled the normal curve. At the third and sixth postprandial hours the percentages were +27.2 and +60, respectively. At the ninth hour, however, the level was still considerably elevated +42.1 per cent. The average curve for the

patients with definite evidence of disease of the liver showed a distinctly different type of curve, which apparently denotes diminished and delayed absorption of ingested fat. The average rise at the third, sixth and ninth postprandial hours was + 89, + 169 and + 226 per cent, respectively.

#### CONCLUSION

Fat absorption curves of normal men and of patients with disease of the liver were sufficiently characteristic and different to be of aid in determining the status of the function of the liver.

# Progress in Internal Medicine

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## DISEASES OF THE HEART

A REVIEW OF CONTRIBUTIONS MADE DURING 1934

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AND

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There has not been a major contribution to the knowledge of heart disease during 1934. Minor advances have been made, however, and some recent gains consolidated. We cannot here review adequately all that has been done, it must suffice merely to indicate certain trends and to cite some of the more interesting publications. While a few of the reports seem more wonderful than probable, we have usually avoided an especially critical attitude because the newness of the work prevents mature conclusion. When convenient for the purpose of continuity or completeness, reference is made to reports published previous to 1934.

### PHYSIOLOGY AND EXPERIMENTAL PATHOLOGY AND PHARMACOLOGY

Cannon<sup>1</sup> outlines the development of the knowledge concerning the chemical mediators of nervous impulses. It may be taken as an established fact that the vagus nerve exerts its inhibitive action on the heart by liberating a substance indistinguishable from acetylcholine and that the sympathetic nervous system exerts its stimulative action by liberating a substance called sympathin, indistinguishable from epinephrine. Many investigators have extended the knowledge in matters related to these fundamental concepts.

Rosenblueth and Simeone,<sup>2</sup> in studying the effects of the vagus and sympathetic nerves on the heart rate in the cat, showed that a given stimulation of the decelerator nerves induces the same percental degree of slowing, independently of whether the accelerators are excited or not, and that a given stimulation of the accelerators evokes a given percental increase of the heart rate which is independent of decelerator excitation.

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From the Cardiac Clinic, Massachusetts General Hospital

1 Cannon, W B. The Story of the Development of Our Ideas of Chemical Mediation of Nerve Impulses, *Am J M Sc* **188** 145, 1934

2 Rosenblueth, A, and Simeone, F A. The Interrelations of Vagal and Accelerator Effects on the Cardiac Rate, *Am J Physiol* **110** 42, 1934

The effects of simultaneous excitation of the accelerator and decelerator nerves are the result of both influences, the two effects occur independently, as if each set of nerves were acting alone. The results not only are consistent with the theory of chemical mediation of autonomic nerve impulses but show that the two mediating substances act on the pacemaker and that the rate of production and of destruction of each of the substances is not modified by the presence of the other.

Eccles and Hoff have made an important contribution to the study of the rhythm of the heart beat.<sup>2a</sup> An attempt was made to investigate systematically the behavior of the pacemaker of the heart under experimental conditions designed to elucidate the nature of the physiologic processes underlying its rhythmic production of impulses. In the first part of the work the pacemaker was located as accurately as possible, its recovery of excitability after a normal beat was determined, and the effect on the recovery curve of vagal slowing and of accelerantes quickening was investigated. The second and third parts deal with the effect of late and early premature beats on the rhythm of the pacemaker.

Brown and Eccles<sup>3</sup> have studied the action of controlled vagal inhibition of the heart beat in cats. They concluded from their experiments that the right and left vagi are distributed independently to the pacemaker—i.e., there is no appreciable convergence of their pathways in the ganglions or elsewhere—and that the acetylcholine substance is liberated by the stimulus from a preformed store, and if a delay occurs it may be due to the time taken in the mobilization of the preformed acetylcholine substance. They offer the provisional hypothesis that the rhythmic mechanism of the pacemaker sets up a beat when its excitement reaches a certain threshold of intensity. Acetylcholine substance inhibits by acting as a quantitative antagonist to this excitement, the setting up of a beat being delayed until the excitement is built up to such an intensity that the inhibited excitement attains a threshold value.

The more intimate details concerning the manner in which these chemical mediators are held and liberated are not yet known. While earlier workers found that heart muscle killed and extracted during stimulation of the vagus nerve yielded a substantially larger proportion of acetylcholine substance, Vartiainen,<sup>4</sup> using an improved technic, found no such increase. He points out that the quantity of acetylcholine sub-

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2a Eccles, J. C., and Hoff, H. E. Rhythm of Heart Beat. Location, Action Potential and Electrical Excitability of the Pacemaker, *Proc Roy Soc London*, s B **115** 327, 1934.

3 Brown, G. L., and Eccles, J. C. The Action of a Single Vagal Volley on the Rhythm of the Heart Beat, *J Physiol* **82** 211, 1934, Further Experiments on Vagal Inhibition of the Heart Beat, *ibid* **82**:242, 1934.

4 Vartiainen, A. Does Vagus Stimulation Cause an Increase in the Acetylcholine Content of Heart Muscle? *J Physiol* **82**:282, 1934.



stance which would have to be liberated to produce the physiologic effect would be so small in relation to the total amount obtainable by extraction that the available methods would not be sufficiently accurate to detect the change

Closely related to the aforementioned studies are those concerning the action of sympathomimetic substances and the cholines with regard to cardiac irregularities

Meek and Seevers <sup>5</sup> have amplified previous studies of the effects of ephedrine on the heart. When an appropriate dose of ephedrine is injected into an unanesthetized dog the first stage is a rise of blood pressure which leads to reflex bradycardia. During the second stage there is either a slow return to the normal rate or the development of arrhythmias. The latter are "escape" phenomena, the normal pacemaker is temporarily inhibited to a level below the automatic capacity of the lower centers and beats arise from the auriculoventricular node, the bundle or its branches. The third stage is characterized by a stimulating action on the automatic tissues which is enhanced by previous atropinization and declared by rapid ectopic rhythms. Larger doses of ephedrine act as depressants. A preliminary dose of sodium barbital will protect against the development of the arrhythmias by ephedrine. This protective action of barbital, the authors believe, is due to its depressant action on the vagus nerve and specialized conduction pathways of the heart.

Nathanson <sup>6</sup> has utilized a unique method for the study of the action of drugs on the impulse-initiating property of the human heart. Studying patients in whom carotid sinus pressure produced cardiac standstill, he found that epinephrine abolished the standstill by stimulating a new center of impulse formation in the ventricles, ephedrine acted similarly when given intravenously or in large doses by mouth.

Hoff and Nahum <sup>7</sup> have studied the action of epinephrine in the production of ventricular rhythms in cats. They emphasize that benzene and chloroform sensitize the ventricular myocardium to the epinephrine in the body and in this way so increase the ventricular rhythmicity that abnormal rhythms appear. These ventricular rhythms are readily abolished by acetyl- $\beta$ -methylcholine chloride, administered in appropriate doses, which depresses not only the rhythmicity of the pace-

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5 Meek, W. J., and Seevers, M. H. The Cardiac Irregularities Produced by Ephedrine and a Protective Action of Sodium Barbital, *J. Pharmacol. & Exper. Therap.* **51** 287, 1934.

6 Nathanson, M. H. Further Observations on the Effect of Drugs on Induced Cardiac Standstill, *Arch. Int. Med.* **54** 111 (July) 1934.

7 Hoff, H. E., and Nahum, L. H. The Rôle of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl- $\beta$ -Methylcholine Chloride, *J. Pharmacol. & Exper. Therap.* **52** 235, 1934.

maker and auricle where vagal endings are known to exist, but also that of the ventricular myocardium

Dikshit<sup>8</sup> has attempted to support the experiments of Brow, Long and Beattie regarding the central origin of cardiac premature beats. He produced cardiac irregularities in cats by central vagal stimulation, clamping both carotid arteries, and the intraventricular cerebral injection of acetylcholine, caffeine or nicotine. The fact that the minimum effective intraventricular cerebral dose of caffeine was one fifth of the corresponding intravenous dose he considers strong evidence against the theory that the drug acts on any tissue outside the central nervous system. Sodium barbital given intracerebrally or intravenously was found to lessen the incidence of or abolish the cardiac irregularities provoked by the caffeine. The possibility of a similar mode of action in human beings is considered. He records experiments on a man in whom sodium barbital markedly lessened the number of ectopic beats. By analogy to the results in the cat he considers that the extrasystoles were probably of central origin. While this analogy will support his theory it will not permit conclusion.

The clinical application of some of this knowledge has already been made. The vagomimetic cholines have been used in the control of abnormal rhythms, and the stimulating action of epinephrine is well known. Also, the barbital compounds may prevent the occurrence of ectopic beats or rhythms, which have been shown to occur frequently during anesthesia.

Van Liere, Crisler and Hall,<sup>9</sup> using dogs under sodium barbital anesthesia, measured the area of the heart by means of roentgen rays before and after cardiac dilatation was produced by the administration of pure nitrogen. When these animals were again subjected to similar grades of anoxemia after the intravenous injection of 0.25 cc. of tincture of digitalis per kilogram of body weight the amount of cardiac dilatation was appreciably lessened. The authors feel that digitalis acts directly on the cardiac musculature so that the tone of the heart is increased and contraction is more complete. These observations afford additional support to the clinical practice of giving digitalis to patients with normal rhythm in the early stages of heart failure.

Bellet, Johnston and Schechter<sup>10</sup> determined the tolerance of dogs to digitalis at various intervals of time after ligation of the left anterior

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8 Dikshit, B. B. The Production of Cardiac Irregularities by Excitation of the Hypothalamic Centers, *J. Physiol.* **81** 382, 1934.

9 Van Liere, E. J., Crisler, G., and Hall, J. E. The Effects of Digitalis on Acute Cardiac Dilatation Produced by Anoxemia, *J. Pharmacol. & Exper. Therap.* **52** 408, 1934.

10 Bellet, S., Johnston, C. G., and Schechter, A. Effect of Cardiac Infarction on the Tolerance of Dogs to Digitalis, *Arch. Int. Med.* **54** 509 (Oct.) 1934.

descending coronary artery in comparison with tolerance in a normal control series. Tincture of digitalis diluted twenty times with physiologic solution of sodium chloride was given by continuous infusion into the femoral vein at a rate of 0.025 cc per kilogram of body weight per minute. This rate of administration was sufficient to cause the death of normal dogs in from thirty to forty-five minutes. Dogs in which standardization was effected within one-half hour after ligation showed no diminution in tolerance to digitalis as compared with those in a control group. During the stage from acute to subacute infarction tolerance was diminished from 20 to 30 per cent, while in the animals with chronic infarction (with standardization from six weeks to six months after ligation of the coronary artery) the tolerance was less than that of the normal animals but higher than that of the group with subacute infarctions. This finding of the slight decrease in tolerance to digitalis in animals should not, however, be interpreted as evidence contraindicating the use of digitalis in man when congestive heart failure supervenes in acute, subacute or chronic myocardial infarction. There is much more chance of saving than of losing life by the proper use of this drug in these cases.

Kountz, Pearson and Koenig<sup>11</sup> revived human hearts shortly after death and measured the flow into the coronary arteries during vagal or sympathetic stimulation and the administration of drugs. In the strongly beating heart stimulation of the peripheral end of the vagus nerve slowed the heart rate and increased the flow into the coronary arteries while sympathetic stimulation increased the heart rate and decreased the flow. In four instances there was complete dissociation of the ventricles and auricles, under this circumstance stimulation of the nerves did not change the ventricular rate, but stimulation of the vagus nerve decreased the coronary flow and stimulation of the sympathetic nerve increased the flow. These results are of special interest and are at variance with the findings of Anrep and his collaborators and others. Anrep found that stimulation of the vagus nerve in dogs decreases, while the stimulation of the sympathetic nerve increases, coronary flow and that changes in the rate have no appreciable influence. Kountz and his co-workers<sup>11</sup> tested the matter further and found that atropine, which increases the rate and has but little effect on the strength of contraction, diminishes the coronary flow, while pilocarpine, which decreases the heart rate without change in the force of contraction, increases the flow. In hearts arrested in increased tone

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11 Kountz, W. B., Pearson, E. F., and Koenig, K. F. Observations on the Effect of Vagus and Sympathetic Stimulation on the Coronary Flow of the Revived Human Heart, *J. Clin. Investigation* **13** 1065, 1934.

(alkaline perfusate) stimulation of the vagus nerve increased the coronary perfusion flow while sympathetic stimulation in two instances decreased it. In hearts arrested in decreased tone (acid perfusate) stimulation of the vagus nerve had no effect on coronary perfusion flow while stimulation of the sympathetic nerve increased it. These workers reached the interesting hypothesis that in man cardiac nerves exert their most important action on coronary flow through changes in the state of the heart muscle and in the heart rate.

In an investigation on the nature of the action of diuretic drugs in normal persons, Blumgart and his collaborators<sup>12</sup> studied the water and salt metabolism and its alterations with the administration of salyrgan (mersalyl), novasurol (merbaphen), euphyllin (theophylline ethylenediamine) and theobromine sodiosalicylate. The 3 normal men chosen for this study were placed in a physical environment kept as constant as possible. A uniform diet and the same measured amounts of water were given at specified times each day. Specimens of urine were collected seven times daily and the constituents carefully analyzed. Certain analyses of stools and of serum were also made, and the rates of glomerular filtration were measured by a modification of the method of Rehberg. The diuretic effects of the four drugs studied were qualitatively similar. All caused an increased output of water, sodium, chloride, potassium and calcium. No significant change occurred in the metabolism of phosphate, sulphate, ammonia or total nitrogen. In general, merbaphen produced a slightly greater effect than the same amount of mersalyl, the xanthine diuretics caused a smaller response than a comparable clinical dose of the mercurial diuretics. Doubling the dose of mersalyl and of merbaphen approximately doubled the duration of the diuresis and approximately trebled its magnitude. The authors concluded that the immediate cause of the diuresis is a relative decrease in tubular reabsorption, the rate of glomerular filtration remains unchanged. This conclusion assumes the validity of the method of Rehberg. The important source of the increased output of water and salt is the body fluids, the intracellular loss being only 10 per cent or less of the total. Neither the xanthine nor the mercurial diuretics caused measurable changes in the specific gravity or in the sodium chloride content of the blood serum during the height of, or after, diuresis. These results are opposed to the opinions of investigators who believe that diuresis following the administration of diuretic drugs is initiated by the kidneys in response to measurable changes in some of the constituents in the blood.

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<sup>12</sup> Blumgart, H. L., Gilligan, D. R., Levy, R. C., Brown, M. G., and Volk, M. C. Action of Diuretic Drugs. I. Action of Diuretics in Normal Persons, *Arch. Int. Med.* **54**:40 (July) 1934.

While space prohibits details we should like to mention by title some interesting papers on respiratory arrhythmia<sup>13</sup> and on the creatine content of the myocardium<sup>14</sup>

### ELECTROCARDIOGRAPHY

The three leads usually employed in electrocardiography interpret the potential differences arising in the heart, projected in a single plane along the sides of an imaginary equilateral triangle. The value of leads taken in another plane has long received consideration, but only during the past few years have significant studies been carried out. The technic of precordial leads and the characteristics of the normal curves have been described and certain abnormal curves interpreted. While most of the information which can be offered by the electrocardiogram is shown in the usual leads, the precordial leads are proving an aid in the localization of certain myocardiac defects in the heart and rarely in showing such a defect not evident in the standard leads. It may be mentioned that in leading from the precordium variations in the resulting curves occur when the lead point is shifted. Most workers therefore consider multiple derivations necessary. It is readily apparent that a large amount of information must be collected on the normal and abnormal curves before a final appraisal of this procedure can be made.

Master<sup>15</sup> adds the information gained by a study of the precordial lead in 104 normal adults. The anterior electrode was placed near the lower end of the sternum just to the left of the midline, and the posterior electrode was directly opposed behind. This approximates the position of the exploring electrode used in obtaining the so-called lead IV. Figure 1 in Master's paper<sup>15</sup> is a typical illustration. In his series the P wave is negative, not more than  $-1.5$  mm, and is usually followed by an end-deflection above the iso-electric level. The PQ interval averages 0.15 second. The QRS group is always diphasic (first phase downward, second phase upward) and never notched or slurred. Its duration is 0.09 second. The absence of the Q wave (first phase of the QRS group, negative) or of the R wave (second phase of the QRS

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13 Ziegler, K. Die respiratorische Arrhythmie im Alter, *Ztschr f Kreislaufforsch* **26** 1, 1934. Hermann, H., Jourdan, F., and Vial, J. De l'influence des mouvements respiratoires sur le tonus et l'excitabilité du centre cardio-moderateur bulbaire, *J de physiol et de path gen* **32** 343, 1934.

14 Cowan, D. W. The Creatine Content and the Weight of the Ventricles in Experimental Hyperthyroidism and After Thyroparathyroidectomy, *Am J Physiol* **109** 312, 1934. The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, *Am Heart J* **9** 378, 1934. Seecof, D. P., Linegar, C. R., and Myers, V. C. The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, *Arch Int Med* **53** 574 (April) 1934.

15 Master, A. H. The Precordial Lead in One Hundred and Four Normal Adults, *Am Heart J* **9** 511, 1934.

group, positive) is definitely abnormal. The Q wave averages  $-5.3$  mm and the R wave,  $+10.7$  mm. No Q wave less than  $-1.5$  mm and no R wave less than  $+2.5$  mm was observed. The RT transition is below the iso-electric level and occasionally is just iso-electric. A positive RT transition or one that is more than 2 mm below the iso-electric level is definitely abnormal. The T wave is always inverted and usually is less than  $-6$  mm.

Wood and Wolferth<sup>16</sup> have reported 7 cases in which huge T waves (13 mm or more in amplitude) were demonstrated in the precordial leads which decreased in amplitude at a later date. Symptoms in these cases pointed to occlusion of a small branch or partial occlusion of a large coronary vessel. The usual leads indicated acute or subacute cardiac infarction in each instance.

Lian<sup>17</sup> and his collaborators have employed precordial leads which were governed by anatomic considerations of the heart cavities. They have endeavored to study auricular and ventricular derivations and to divide each of them into left and right varieties. Electrodes placed on the manubrium and at the sternal extremity of either the third or the fifth right intercostal space yield the most satisfactory auricular curves, which, they believe, correspond principally to the right auricle. They give data on illustrative cases of auricular fibrillation and flutter in which the usual leads failed to show, or did not show properly, the auricular waves, whereas the precordial leads showed these waves indisputably. They attempted, relatively unsuccessfully, to obtain left auricular leads. A series of tracings were taken which, they believe, record predominantly left ventricular events by leaving one electrode fixed over the apex of the heart while the second was moved circumferentially toward the left and then toward the right, a point over the xiphoid was chosen for the fixed electrode in obtaining tracings showing chiefly right ventricular events. The characteristics of electrocardiograms so obtained from normal and abnormal hearts are detailed. In a study of persons with heart disease the information obtained from precordial derivations was confirmatory of that derived with the usual leads. In persons with intraventricular block the precordial tracings showed pure or predominant right or left ventricular preponderance. In instances of ventricular extrasystoles the workers were unable to conclude whether their origin was in the right or in the left ventricle.

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16 Wood, F. C., and Wolferth, C. C. Huge T-Waves in Precordial Leads in Cardiac Infarction, *Am Heart J* 9 706, 1934.

17 Lian, C., Merklen, F. P., and Odinet, J. Les derivations précordiales en électrocardiographies. I. Technique et derivations précordiales auriculaires, *Arch mal du coeur* 27 189, 1934, Les derivations précordiales en électrocardiographies, II. Les derivations ventriculaires, *ibid* 27 269, 1934.

In taking standard electrocardiographic leads, Wilson and his collaborators<sup>18</sup> point out that electrodes are placed approximately equidistant from the heart and that, on the average, their potential variations are of about the same magnitude and influence equally the resultant curves. When the exploring electrode is placed on the precordium and the indifferent electrode is placed on the left leg the chief features of the curves so taken are determined by the potential variations of the mobile electrode. However, the potential variations of the indifferent electrode cannot always be regarded as negligible. To reduce or eliminate them and make precordial curves more nearly comparable to those obtained by direct and semidirect leads in animals, they designed leads to record the potential variations of a single electrode. Leads from both arms and the left leg are connected through separate noninductive resistances to a central terminal which serves as the indifferent electrode. This central terminal and the exploring electrode are connected to the input terminals of a vacuum tube with a balanced plate circuit in which the string galvanometer is inserted. Theoretical considerations and experiments on a model indicate that under these circumstances the potential variations of the central terminal are negligible. The curves obtained by leading from an exploring electrode in contact with any part of the body to the central terminal represent the variations in potential produced by the heart beat in the region in contact with the exploring electrode.

Employing this method, Wilson and his co-workers<sup>19</sup> obtained precordial leads in 3 cases in which standard electrocardiograms showed a QRS interval measuring 0.12 second or more, narrow R deflections and broad S deflections in lead I, while lead III showed a narrow downward deflection synchronous with R in lead I and a broad upward deflection synchronous with S in the same lead. Leads from the right side of the precordium in these cases showed a very late chief upstroke while leads from the left side of the precordium showed an early chief upstroke approximately synchronous with the peak of R in lead I. These curves were strikingly similar to those obtained by the same method of leading after section of the right branch of the bundle of His in dogs. In dogs there is great similarity between curves obtained by direct lead from the heart and precordial curves, which strongly supports the view that the ventricular complex in precordial leads in man is similar in general outline and with regard to the position of the

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18 Wilson, F. N., Johnson, F. D., Macleod, A. G., and Barker, P. S. Electrocardiograms That Represent the Potential Variations of a Single Electrode, *Am Heart J* 9:447, 1934.

19 Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S. The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *Am Heart J* 9:459, 1934.

chief upstroke in the QRS interval to the curves that would be obtained by leading directly from the epicardial surface of the subjacent portions of the cardiac wall. It is concluded, therefore, that clinical curves of the kind described are due in all probability to right bundle branch block.

In another report Wilson and his colleagues<sup>20</sup> describe 3 cases in which the standard electrocardiograms suggested an unusual variant of the kind seen in left bundle branch block. In lead I all the ventricular deflections were small, there was a conspicuous S deflection and T was usually flat or upright. In leads II and III the ventricular deflections are similar in all respects to those seen in left bundle branch block. In precordial leads using a central terminal for the indifferent electrode, there was clear indication that in each instance the conduction defect was on the right side, and similar curves were obtained in right bundle branch block in the dog.

Utilizing this newer knowledge, Bayley<sup>21</sup> analyzed the examples of bundle branch block in Wilson's clinic and found 70 curves of complete right bundle branch block and 103 curves showing the characteristics of left bundle branch block. Thus, previous ideas concerning the rarity of right bundle branch block are no longer tenable. In a comparison of the etiologic factors responsible for block of the right or left side no significant differences were noted except with regard to rheumatic heart disease, in which the defect was found in 7 of 8 cases to be on the right.

While the relationship between the final ventricular deflection, T, and coronary heart disease has been extensively investigated, a similar relationship with regard to changes in the initial ventricular deflections, QRS, has only recently received attention. During the past year additional studies<sup>22</sup> have emphasized previous declarations of the diagnostic value of these changes in the QRS complex. Two types of QRS deflections are held to be characteristic of coronary heart disease, the  $Q_1$  and  $Q_3$  types. In the former, according to Durant,<sup>22a</sup> Q in lead I must measure at least 1 mm and be at least one-fifth as large as the largest

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20 Wilson, F. N., Johnston, F. D., and Barker, P. S. Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *Am Heart J* **9** 472, 1934.

21 Bayley, R. H. The Frequency and Significance of Right Bundle-Branch Block, *Am J M Sc* **188** 236, 1934.

22 (a) Durant, T. M. The Initial Ventricular Deflection of the Electrocardiogram in Coronary Disease, *Am J M Sc* **188** 225, 1934. (b) France, R. The Large Q Wave in Lead III of the Electrocardiogram, *ibid* **187** 16, 1934. (c) Winternitz, M. The Initial Complex of the Electrocardiogram After Infarction of the Human Heart, *Am Heart J* **9** 617, 1934. (d) Barnes, A. R. Correlation of Initial Deflections of Ventricular Complex with Situation of Acute Myocardial Infarction, *ibid* **9** 728, 1934. (e) Bellet, S., and Johnston, C. G. The Effect of Coronary Occlusion upon the Initial Phase of the Ventricular Complex in Precordial Leads, *J Clin Investigation* **13** 725, 1934.



R wave in any lead, there must be a definite R wave in lead I measuring less than 5 mm. In the  $Q_3$  type, Q in lead III must measure at least one-half as much as the largest R in any lead, and in lead 2, Q must measure at least one-fourth as much as R, curves showing right axis deviation must be excluded. The  $Q_1$  type is commonly associated with acute or healed infarcts involving the anterior wall or apical portion of the heart, while the  $Q_3$  type is commonly associated with infarction of the posterior wall of the heart. Because QRS is not as variable in form and direction as T, the lasting character of these QRS changes has been emphasized. It is necessary to mention that in a considerable number of cases yielding QRS waves of the types mentioned no coronary disease can be found, the QRS changes alone should not be relied on too strongly, especially in lead III. The criteria proposed by Durant<sup>22a</sup> narrow considerably the field within which so-called  $Q_3$  may be judged to be abnormal, in contrast to the loose references to so-called coronary  $Q_3$  waves current recently.

By means of records of the heart sounds and apex cardiograms Lewis<sup>23</sup> has studied patients in whom bundle branch block was present. When these results were correlated with certain physical findings he concluded that the latter could not be related to the bundle branch block itself or to asynchronism of the ventricles.

Lian, Golblin and Barage<sup>24</sup> have reinvestigated the diagnostic value of the relation between the duration of systole and that of diastole as shown in the electrocardiogram, a matter in which there is not univocal conclusion. They established normal values based on the duration of systole and diastole at varying heart rates in healthy subjects. A formula was devised for practical use in determining the duration of systole at a given heart rate. In hypertensive heart disease they found that a manifest cardiac insufficiency can exist without lengthening the ventricular systole, but if the systole is lengthened serious heart disease is invariably present. Similar conclusions were reached with regard to valvular heart disease.

Bruno<sup>25</sup> has uniquely employed the electrocardiograph in estimating the efficiency of the various resuscitation methods, particularly the different forms of artificial respiration and the various forms of medicinal and mechanical cardiac stimulants. The electrocardiogram provides a means of registering cardiac activity when clinical signs are inadequate.

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23 Lewis, J. K. Nature and Significance of Heart Sounds and of Apex Impulses in Bundle Branch Block, *Arch Int Med* **53** 741 (May) 1934.

24 Lian, C., Golblin, V., and Barage. Diagnostic et valeur semeiologique de l'allongement et du raccourcissement de la systole ventriculaire. La constante systolo-diastolique, *Presse med* **42** 787, 1934.

25 Bruno, C. Elektrokardiographische Kontrolle des Scheintodes und der Wiederbelebungs-moglichkeiten, *Munchen med Wchnschr* **81** 1225, 1934.

Pezzi<sup>26</sup> studied what he believed to be an odd phenomenon of the electrocardiogram characterized by a special wave appearing below the descending limb of the R wave. In most of the illustrations which he has offered, however, this special wave is not of auricular origin as he maintains but is of ventricular origin and characteristic of aberration of the QRS waves such as commonly occurs in bundle branch block. This misinterpretation throws out his reasoning, which would otherwise have been interesting, about the problem of the physiopathology of the auriculoventricular node and bundle with particular reference to Géraudel's<sup>27</sup> theories.

#### ROENTGENOLOGY

Roesler<sup>28</sup> reemphasizes the fact that the present status of roentgenologic measurement of the heart, with its common limitation to one plane, is unsatisfactory. To judge better the volume of the heart he determined the anteroposterior dimension of the heart as seen in the lateral view in 150 healthy persons. These figures were correlated with certain others of the cardiac diameters obtained in anterior and oblique views. He found that the average anteroposterior diameter of the heart is 73 per cent of the average transverse diameter and 66.3 per cent of the average oblique diameter. A close relationship was found between the weight of the body and the anteroposterior diameter as well as the transverse diameter. Height affects the diameters only if the weight of the body increases correspondingly. In certain persons the heart deviates from the average type by being flatter, broader and longer, while in others it is deeper, narrower and shorter.

Wilson<sup>29</sup> believes that the usual roentgenologic criteria offer little assistance in differentiating between the normal and the moderately enlarged heart in the child. She proved the inability of the usual indexes (cardiothoracic index and surface area) to distinguish with any degree of frequency the normal from the abnormal heart in a series of 504 cases. When the heart was studied in several planes the abnormal heart was distinguished from the normal in an overwhelmingly large percentage. Of special importance was the size of the angle of clearance of the left ventricle determined by rotating the subject from the left anterior oblique position until the lower dorsal border of the heart was

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26 Pezzi, C. L'onde P du complexe ventriculaire initial sur les traces électriques avec troubles du rythme, *Arch. d. mal. du coeur* **27** 201, 1934.

27 Géraudel, E. Une conception nouvelle de la dissociation auriculo-ventriculaire, la double commande, *Presse med.* **42** 814, 1934.

28 Roesler, H. The Relation of the Shape of the Heart to the Shape of the Chest, *Am. J. Roentgenol.* **32** 464, 1934.

29 Wilson, M. G. Clinical Radioscopic Studies of the Heart in Children. Roentgenologic Criteria of Cardiac Enlargement, Size of Angle of Clearance of Left Ventricle as Criterion of Ventricular Enlargement, *Am. J. Dis. Child.* **47** 750 (April) 1934.

clearly separated from the vertebral column. The degree of rotation at which this is observed is arbitrarily designated the angle of clearance.

The determination of the volume, shape and action of the chambers of the heart and the aorta is the chief goal of the cardiac roentgenologic examination. Because the heart is a moving, irregular, three-dimensional body great limitations are encountered. A roentgenogram shows the cardiac silhouette in a single plane only, and fluoroscopy does not allow an appreciation of the finer details of movement. Cinematograph studies would be highly desirable, but they have not yet proved feasible. The kymographic method has made practical, however, two-dimensional registration, which Vaquez places in the category of optical inscriptions. The kymograph consists of a grid constructed of lead strips separated by narrow openings placed between the patient and the film-carrier. During exposure either the film-carrier or the grid is moved at a specified rate. With a moving grid the continuity of the contour of an organ is obtained while a moving film shows the contour of an organ in step-like stages. One film records the results of a continuous series of exposures. Kymography is proving a useful complement to the usual roentgenologic methods and during the past year has been studied extensively.<sup>30</sup> It promises to aid in the functional and anatomic study of the normal and the abnormal heart. It will probably allow considerations of contractility and tonus and better differentiation of the several cardiac chambers and their movements and should materially aid in the diagnosis of pulmonary congestion and pericarditis and in the differential diagnosis of mediastinal tumors and aneurysm, especially with improvement of apparatus and technique.

Some interesting roentgenologic studies of intracardiac calcifications have been made.<sup>31</sup> Not only does this method furnish objective

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30 Delherm, L., Thoyer-Rozat, P., and Fishgold. L'exploration fonctionnelle du cœur par la radiokymographie, *J de radiol et d'electrol* **18** 505, 1934. Zierach, H.-J. Untersuchungen über die Konstanz der röntgenographisch darstellbaren Bewegungen des Herzens, *Fortschr a d Geb d Röntgenstrahlen* **50** 16, 1934. Nolte, F. A. Ueber die Veränderung der Herzform und- grosse unter der Einwirkung intrapulmonaler Drucksteigerung nach kardiokymographischen Untersuchungen (Das Kardiokymogramm im Valsalvaschen Versuch), *ibid* **50** 211, 1934. Stumpf, P. Die kymographische Analyse der Bewegungen des Herzens, *ibid* **49** 211, 1934. Zdansky, E., and Ellinger, E. Röntgenkymographische Untersuchungen am Herzen, *ibid* **49** 240, 1934. Cignolini, P. Die Röntgenkymographie mit unterbrochenem Schlitz, *ibid* **49** 224, 1934. Hirsch, I. S., and Schwarzschild, M. The Simultaneous Recording of Cardiac Movements and Sounds by the Roentgen Ray, *Acta radiol* **15** 101, 1934.

31 Bishop, P. A., and Roesler, H. The Roentgenologic Diagnosis of Intracardiac Calcifications, *Am J Roentgenol* **31** 1, 1934. Wosika, P. H., and Sosman, M. C. The Roentgen Demonstration of Calcified Coronary Arteries in Living Subjects, *J A M A* **102** 591 (Feb 24) 1934. Sosman, M. S., and Wosika, P. H. The Position of the Heart Valves and Their Relation to the Anterior Chest Wall in Living Subjects with Abnormal Hearts, *Am Heart J* **10** 156, 1934.

pathognomonic evidence of certain changes in the heart but it adds to the knowledge of cardiac anatomy and physiology

### INCIDENCE AND ETIOLOGY OF HEART DISEASE

The "appalling increase in the death rate from heart disease" has been a favored subject for discussions and addresses. The sources for material have usually been "clinical impressions" or actuarial figures improperly corrected. Cohn and Lingg<sup>32</sup> have studied certain statistics on the death rate in the registration area comprising the states of New England, New York, New Jersey, Indiana and Michigan and the District of Columbia. Curves representing the death rate at each decade from 1900 to 1930 were constructed. For the infectious diseases the rate has fallen in every decade. For heart disease, before the age of 40 the rates have steadily fallen since 1900. In the later decades the death rate has increased distinctly for "chronic cardiac diseases" and "diseases of the arteries" and less in the three highest decades (70 and upward) for "chronic nephritis" and "cerebral hemorrhage and softening of the brain" and has fallen sharply for "senility." If the group of circulatory and renal diseases is studied as a whole with a view to ignoring fashions in diagnosis, an increase in the death rate is observable beginning with the sixth decade, but the increase is slight in comparison with what have been regarded as the facts based on a consideration of "chronic cardiac diseases" alone. The rise in the rate for the circulatory diseases, relatively small though it is, depends largely on the fall in the rate for infectious diseases—not the fall, as has often been supposed, in early life, but the fall in those very decades in which a rise in the mortality from circulatory diseases has taken place. A consequence of this analysis is that belief in the theory that "stress and strain" of life accounts for most of the increase in the death rate for the cardiac diseases is unnecessary.

### RHEUMATIC HEART DISEASE

Paul and his collaborators<sup>33</sup> have sought further proof of the clinical impression that rheumatic fever finds its highest incidence among persons living under poor hygienic and urban conditions. They compared the incidence of rheumatic heart disease in pupils between the ages of 4 and 18 years in public and private schools of New Haven, Conn., and its environs. The incidence of rheumatic heart disease in a single large public school in one of the poorer districts of the city was 48.1 per thou-

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<sup>32</sup> Cohn, A. E., and Lingg, C. Heart Disease from the Point of View of the Public Health, *Am Heart J* 9:283, 1934.

<sup>33</sup> Paul, J. R., Harrison, E. R., Salinger, R., and De Forest, G. K. The Social Incidence of Rheumatic Heart Disease. A Statistical Study in New Haven School Children, *Am J M Sc* 188:301, 1934.

sand This proved to be one and one-half times as high as that found in a public school in one of the better districts of the city and eight times as high as that found among the smaller group of pupils from private schools who came from the best districts The average incidence of rheumatic heart disease among pupils attending two urban public schools was about twice that recorded among pupils of a similar age group who attended suburban and rural public schools These findings are in accord with observations made in 1924 by Faulkner and White<sup>33a</sup>

Great efforts have been made without success to establish definitely the relationship between streptococcic infection and rheumatic fever A few of the recent investigations along this line may be mentioned

Rinehart and his associates<sup>34</sup> have presented experimental data which they believe offer evidence that rheumatic fever may be the result of the combined influence of scurvy and infection They found that when guinea-pigs are subjected to scurvy and a localized infection with beta hemolytic streptococcus striking lesions are produced, while lesions of similar significance are not seen with either agent acting alone In the valves of the heart pathologic changes of a degenerative and proliferative character occur which resemble those of acute rheumatic fever While typical Aschoff bodies were not seen in the myocardium the authors describe changes similar to those in the Aschoff reaction and lesions resembling the "fibrinoid degeneration" which Klinge considered characteristic of rheumatic fever They describe changes in the joints and elsewhere which have striking pathologic similarities to those of rheumatic fever These interesting experiments must await confirmation before a final opinion can be given, it cannot be safely argued that rather similar pathologic responses declare a common etiologic agent

Weinstein and Styron<sup>35</sup> made cultures from the nasopharyngeal swabbings from 321 patients, 46 per cent of whom suffered from active or chronic rheumatic fever and the remainder of whom formed a control group which included normal persons and patients suffering from conditions unrelated to rheumatic fever The authors discovered that *Streptococcus haemolyticus* is present no more frequently or abundantly

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33a Faulkner, J M, and White, P D The Incidence of Rheumatic Fever, Chorea and Rheumatic Heart Disease, *J A M A* **83** 425 (Aug 9) 1924

34 Rinehart, J F, and Mettier, S R The Heart Valves and Muscle in Experimental Scurvy with Superimposed Infection With Notes on the Similarity of the Lesions to Those of Rheumatic Fever, *Am J Path* **10** 61, 1934 Rinehart, J F, Connor, C L, and Mettier, S R Further Observations on Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, *J Exper Med* **59** 97, 1934

35 Weinstein, I, and Styron, N C Bacteriologic Study of Throats in Rheumatic and Nonrheumatic Fever with Special Reference to Hemolytic Streptococci, *Arch Int Med* **53** 453 (March) 1934

in cultures of swabbings from the throats of persons suffering from rheumatic fever than in those of other persons, nor does this streptococcus appear more abundantly in the flora from the throats of patients with acute rheumatic fever than in those of patients with chronic rheumatic heart disease. Green-producing streptococci were present in all the cases of rheumatic heart disease and predominated in 69 per cent, while indifferent streptococci were present in 96 per cent of the cases but did not predominate in any. An effort was made to determine a definite relationship between exacerbations of rheumatic fever and previous infections of the upper respiratory tract with *Str. haemolyticus*. Among 96 patients 37 had an exacerbation of chronic rheumatic heart disease. Of the 37, 18 suffered from an infection of the upper respiratory tract from fifteen to twenty-one days prior to the recrudescence of rheumatic symptoms while 19 had no recognizable preceding infection. Of the 37, 23 had throat cultures which yielded *Str. haemolyticus* three weeks or more prior to the relapse, and 14 had no known occurrence of these organisms, although 9 of the 14 did experience infection of the upper respiratory tract. Whether these 9 patients would have shown *Str. haemolyticus* had more cultures been made at the time of infection is not known. The authors interpret these observations as suggesting a possible relationship between the hemolytic streptococcus and the exacerbations of acute rheumatic fever.

Todd has described an antistreptolysin which is capable of neutralizing the hemolytic substance formed in vitro by hemolytic streptococci. He found an increase in this antistreptolysin in the blood stream of persons recently recovered from infection with *Str. haemolyticus*. Myers and Keefer<sup>36</sup> confirmed Todd's results and found that the titer of the serum of patients with active rheumatoid arthritis was in all respects similar to that of normal persons. While in 33 patients with active rheumatic infection the average titer was greater than in normal persons and about the same as for patients with proved infection with *Str. haemolyticus*, in 7 of these 33 cases the titer was never found to be higher than normal. Myers and Keefer feel justified in questioning the inference that an attack of rheumatic fever is necessarily dependent on a preceding infection with *Str. haemolyticus*.

Tillett and his associates<sup>37</sup> are investigating another means of determining the response of the body to infection with *Str. haemolyticus*.

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36 Myers, W. K., and Keefer, C. S. Antistreptolysin Content of the Blood Serum in Rheumatic Fever and Rheumatoid Arthritis, *J. Clin. Investigation* **13** 155, 1934.

37 Tillett, W. S., Edwards, L. B., and Garner, R. L. Fibrinolytic Activity of Hemolytic Streptococci. The Development of Resistance to Fibrinolysis Following Acute Hemolytic Streptococcus Infections, *J. Clin. Investigation* **13**:47, 1934.

The investigation is concerned with the demonstration that whereas broth cultures of hemolytic streptococci are capable of rapidly liquefying the fibrin clot of normal human plasma, the blood of patients convalescent from infection with *Str haemolyticus* is highly resistant to the fibrinolytic principles. Comparative tests on a series of patients with rheumatic fever have not yet been carried out.

Gross and Ehrlich<sup>38</sup> have studied the genus of Aschoff body found in the interstices of the myocardial bundles. Seven types are delineated, not counting the many possible combination forms. The authors believe that these lesions pass through three stages of development during a period of sixteen weeks following the onset of rheumatic fever, the types of lesions found at each stage are described.

Karsner and Bayless<sup>39</sup> report their studies on the coronary arteries in fifty-six hearts showing Aschoff nodules, controlled with observations on forty nonrheumatic hearts. They found the incidence of intimal fibrosis of the smaller coronary vessels overwhelmingly greater in the rheumatic than in the nonrheumatic hearts and concluded that permanent arterial disease appears early in the course of rheumatic fever. This intimal fibrosis they believe to be progressive and to afford the best explanation for the extensive myocardial fibrosis and scarring.

Rothschild and his associates<sup>40</sup> have tested the clinical impression that myocardial changes rather than valvular defects are probably the immediate cause of cardiac failure in rheumatic heart disease. They investigated the clinical records and autopsy material of 161 cases of rheumatic cardiovalvular disease and correlated by decades the occurrence of heart failure, the degree of valvular damage and the evidence of active rheumatic infection. Of the 161 cases, evidence of acute infection was noted in 106, in 103 of which the patient died of cardiac failure. The authors concluded that the occurrence of heart failure in the first five decades of life in persons who have a valvular defect can, in the majority of instances, be attributed to an active rheumatic infection of the myocardium rather than to the degree of the mechanical defect. Circulatory failure in the later decades of life was found, in the majority of cases, to be precipitated by the expected con-

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38 Gross, L., and Ehrlich, J. C. Studies on the Myocardial Aschoff Body. I. Descriptive Classifications of Lesions, *Am J Path* **10** 467, 1934, II. Life Cycle, Sites of Predilection and Relation to Clinical Course of Rheumatic Fever, *ibid* **10** 489, 1934.

39 Karsner, H. T., and Bayless, F. Coronary Arteries in Rheumatic Fever, *Am Heart J* **9** 557, 1934.

40 Rothschild, M. A., Hergel, M. A., and Gross, L. Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovalvular Disease During the Various Age Periods, *Am Heart J* **9** 586, 1934.

tributory causes. The authors rightly point out the practical application of these observations, which places insistence on suspecting active rheumatic infection as the immediate cause of heart failure in persons under 50 years of age.

#### DIPHTHERITIC HEART DISEASE

Careful correlation between the electrocardiographic and clinical findings in diphtheritic myocarditis has shown<sup>41</sup> that while both methods are important, damage is detected earlier and more frequently by the electrocardiographic method and that it consequently forms a better guide to prognosis and therapy. Anderson<sup>41a</sup> reexamined 15 patients in whom electrocardiographic changes were noted during their attack of diphtheria eight or nine years earlier and found that the changes were permanent in 7.

#### VON GIERKE'S DISEASE (GLYCOGEN-STORAGE DISEASE)

Von Gierke in 1929 reported a unique disease entity, the chief feature of which is massive deposits of glycogen in certain organs. Over 15 proved cases have now been reported which provide the basis for a brief summary.<sup>42</sup>

This disease is a disorder of infancy or childhood and may affect either sex. Its etiology is unknown, but is presumably concerned with defective carbohydrate metabolism allowing the parenchymal cells of certain organs to become infiltrated with glycogen. The distribution of glycogen shows unaccountable vagaries, and while the largest deposition is usually in the heart or liver, other tissues usually hold variable amounts. Intimately associated degenerative or proliferative changes are rare, but various disturbances of body growth may occur. At least

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41 (a) Anderson, M. S. Electrocardiographic Studies on Diphtheric Myocarditis. I Myocarditis in Fatal Diphtheria, *Acta med Scandinav* **84** 253, 1934, II Electrocardiographic Signs of Myocarditis in Moderate and Severe Nonfatal Diphtheria, *ibid* **84** 268, 1934, III Comparison Between the Results of the Clinical and the Electrocardiographical Diagnosis of Myocarditis, *ibid* **84** 297, 1934, IV Subsequent Course of Diphtheric Myocarditis, *ibid* **84** 308, 1934. (b) Behr, W. Ueber Herzscheidungen bei maligner Diphtherie, *Ztschr f Kreislaufforsch* **26** 89, 1934. (c) Berger, W., and Olloz, M. Elektrokardiographische Untersuchungen bei Scharlach und Diphtherie, *Schweiz med Wchnschr* **64** 992, 1934.

42 Humphreys, E. M., and Kato, K. Glycogen-Storage Disease. *Thesaurismosis Glycogenica* (von Gierke), *Am J Path* **10** 589, 1934. Biedermann, H., and Hertz, W. Der Einfluss von Adrenalin und Insulin auf den Kohlehydratstoffwechsel bei Glykogenspeicherkrankheit, *Deutsches Arch f klin Med* **176** 272, 1934. Antopol, W., Heilbrunn, J., and Tuchman, L. R. Enlargement of the Heart Due to Abnormal Glycogen Storage, in von Gierke's Disease, *Am J M Sc* **188** 354, 1934.



some instances of so-called congenital idiopathic cardiac hypertrophy are due to glycogen-storage disease. When the heart is involved signs and symptoms of cardiac failure ensue. No specific treatment is known.

#### ARTERIAL HYPERTENSION

There are a number of pathologic conditions with which hypertension is associated and to which it appears to be secondary. Often, however, it apparently exists without definite relationship to any associated disorder, it is then termed essential hypertension. Essential hypertension is commonly considered, though possibly incorrectly, as a definite entity due to a single cause, and this cause has been widely sought. Numerous theories of the etiology have been offered, most of which involve a factor known to cause secondary hypertension under certain conditions. Two excellent reviews<sup>43</sup> have appeared in English during the past year, and reference may be made to them for critical exposition of recent work. Only a superficial review of a few of the articles appearing last year will be given here.

Cushing<sup>44</sup> again expresses his opinion regarding the rôle of the pituitary gland in certain hypertensive states. He believes that the distinctive cells of the pars intermedia acquire basophilic granules in the processes of maturation and migration into the pars nervosa and that the degree of basophilic infiltration may represent a measure of neurohypophyseal activation. He describes the marked increase in these cells found in instances of pituitary basophilism, eclampsia, essential hypertension and hypertension with atherosclerosis in the aged. From this he concludes that the source of these hypertensive disorders lies in the posterior lobe of the pituitary body. He supports his argument with the discovery by Anselmino and Hoffmann of anti-diuretic and pressor substances (posterior pituitary-like substances) in the blood of eclamptic persons with hypertension. Byrom and Wilson,<sup>45</sup> however, have failed to confirm Anselmino and Hoffmann's claim, and Theobald<sup>46</sup> gives significant evidence to show that eclampsia cannot be explained by postulating hyperfunction of the posterior lobe

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43 Weiss, S. The Etiology of Arterial Hypertension, *Ann Int Med* **8** 296, 1934. De Wesselow, O. L. V. S. Arterial Hypertension (Croonian Lectures), *Lancet* **2** 579, 1934.

44 Cushing, H. Hyperactivation of the Neurohypophysis as the Pathological Basis of Eclampsia and Other Hypertensive States, *Am J Path* **10** 145, 1934.

45 Byrom, F. B., and Wilson, C. The Alleged Pituitary Origin of the Eclamptic and Pre-Eclamptic "Toxaemias" of Pregnancy, *Quart J Med* **3** 361, 1934.

46 Theobald, G. W. The Alleged Relation of Hyperfunction of the Posterior Lobe of the Hypophysis to Eclampsia and the Nephropathy of Pregnancy, *Clin Sc* **1** 225, 1934.

of the pituitary We agree that Cushing's hypothesis has not been proved, but until disproved the opinion of a recognized authority in this field commands consideration

Kylin<sup>47</sup> reaffirms his belief that the significant factor in essential hypertension is hyperfunction of the anterior lobe of the hypophysis, which may be associated with hypofunction of the gonads He contrasts Simmond's cachexia, in which hypofunction of the anterior lobe of the pituitary exists, with essential hypertension Using the output of the gonadotropic factor as an index of prehypophyseal activity, he shows that hypertension is often associated with those conditions which cause an increase in the excretion of the gonadotropic factor By quantitating the excretion of the gonadotropic factor in persons with normal and with increased blood pressure he found a direct relationship between the amount of gonadotropic factor excreted and the severity of the hypertension One cannot gainsay Kylin's arguments, we are inclined to agree that hyperfunction of the hypophysis may be associated with hypertension, but confirmation is lacking that this is the responsible factor in the majority of cases of essential hypertension

Daniel<sup>48</sup> presents an interesting and critical review of various theories with regard to the etiology of essential hypertension with special attention to the hepatobiliary theory The discussion of the hepatobiliary theory begins with many arguments provided to show the predominant rôle played by the chemical regulators of blood pressure He next refers to the numerous clinical observations showing the association of jaundice and lowered arterial tension Reasons are given for his opinion that this is a physiologic attribute and not an argument in favor of the toxic nature of bile To determine the action that bile exercises in the normal state he injected vesicular and refined bile into healthy dogs and noticed a very marked and persistent fall in blood pressure followed by a gradual return to normal Dried refined beef bile was administered orally to 17 patients with essential hypertension for ten days in amounts varying from 1.5 to 3 Gm daily In 10 cases the systolic blood pressure was lowered from 40 to 60 mm of mercury, in 5 the reduction was less but there was subjective improvement, while in 2 there was no appreciable effect The responsible hypotensive substance was sought among the biliary elements The rôle of mucin, the bile pigments and salts, cholesterol and choline was considered, but none of these was shown to be the active substance Daniel believes that

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47 Kylin, E Ueber Prolanausscheidung bei essentieller Hypertonie Beitrag zur Aetiologie des Hochdruckes, *Deutsches Arch f klin Med* **176** 301, 1934, Ueber Kohlehydratumsatz bei essentieller Hypertonie Akromegalie und Simmondsscher Krankheit, *Med Klin* **30** 153, 1934

48 Daniel, I Le rôle du facteur hépato-biliaire dans la genèse de l'hypertension, *Ann de med* **35** 300, 1934

in all probability one must attribute this hypotensive action to certain unknown substances that have their route of elimination via the biliary tract, and he concludes that hepatic dysfunction may be related to variations in the arterial blood pressure

Olmer and Carbonel<sup>49</sup> point out the capital rôle played by the autonomic nervous system in the maintenance of normal arterial pressure and argue that without profound disequilibrium between the sympathetic and the parasympathetic system all the direct or indirect factors believed to cause hypertension are vain because they are immediately compensated for. The authors found support for this view in the fall of blood pressure which occurred in patients with hypertension when atropine and small doses of epinephrine were injected. Similar views are held by investigators<sup>50</sup> in explaining the hypotensive action of a substance isolated from the pancreas by Santenise and considered by him to be the hormone of the parasympathetic system. This substance increases the excitability of the sympathetic system, and one of its specific actions causes a slow, progressive fall in arterial tension.

The depressor action of extracts of various organs has been further investigated and discussed.<sup>51</sup> While it is true that some of these extracts have the power to lower arterial tension, this lowering is slight and certainly ephemeral, and it is doubtful if their therapeutic value in hypertension is greater than that of the nitrites.

The surgical treatment of essential arterial hypertension has been directed toward decreasing the amount of circulatory epinephrine or destroying the vasoconstrictor nerves to vessels or both. The theory that essential hypertension is due to hyperepinephrinemia has not been proved, and the decrease in vascular tonus consequent to the destruction of sympathetic innervation is largely regained either by regeneration of the nerves or by the decreased susceptibility of the denervated vessels to circulating hormones and possibly to other pressor bodies.

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49 Olmer, J, and Carbonel, J. Du rôle du système neuro-vegetatif dans l'hypertension artérielle permanente, *Presse med* **42** 581, 1934.

50 Étienne, G, and Louyot, P. La vagotonine et son action thérapeutique cardio-vasculaire, *Paris med* **1** 401, 1934. Desruelles, M, Léculier, P, and Gardien, M. P. Action de la vagotonine sur la pression artérielle (étude portant sur deux cent malades), *ibid* **1** 446, 1934.

51 Frommel, E, and Zimmet, D. L'importance des produits du métabolisme de l'acide nucléique pour la régulation chimique du système cardio-vasculaire, *Arch d mal du coeur* **27** 65, 1934. Wolf, H. J, and Heinsen, H.-A. Der Einfluss körpereigener Substanzen auf den Blutdruck beim Menschen. III. Die Wirkung von Lacarnol, Myoston, Padutin, "viertem" Stoff (Lange) und Eutonin bei intravenöser Verabreichung, *Ztschr f klin Med* **127** 1, 1934. Felix, J. A Clinical and Experimental Study of the Action of Tissue Extracts on the Circulatory System, *Acta med Scandinav* **83** 328, 1934.

The DeCourcys and Thuss<sup>52</sup> have removed from two thirds to three fourths of each adrenal gland in 8 cases of hypertension. They report that the symptoms of hypertension have disappeared and that the blood pressure was lowered on the average from 70 to 90 mm of mercury systolic and from 40 to 50 mm diastolic in each case.

Adson and Brown<sup>53</sup> treated a patient with malignant hypertension by bilateral section of the anterior spinal nerve roots from the sixth thoracic to the second lumbar inclusive, following the operation there was a definite drop in the blood pressure.

Craig and Brown<sup>54</sup> treated 5 patients with hypertension by unilateral or bilateral resection of the splanchnic nerves. While the fall in blood pressure was not great there was a striking reduction in the pressor response to cold in 3 patients with subjective improvement.

#### DISSECTING ANEURYSM OF THE AORTA

Dissecting aneurysm of the aorta is an uncommon disease rarely diagnosed clinically, in which a breach in the wall allows the extension of the blood between the layers. This condition carries an added interest in the difficulty with which it is differentiated from angina pectoris or acute cardiac infarction. The recent extension of the knowledge in this regard<sup>55</sup> will undoubtedly lead to a more frequent clinical recognition.

Shennan<sup>55a</sup> has written a monograph detailing the clinical features and pathologic changes in cases of dissecting aneurysm of the aorta. The first part is a historical introduction. The second part is a complete report of 17 of the 28 cases investigated by the author which illustrate all varieties of dissecting aneurysm except the sacculate. In the third part 500 cases are analyzed, including the 17 described in part 2. The fourth part comprises the summary and conclusions.

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52 DeCourcy, J. L., DeCourcy, C., and Thuss, O. Subtotal Bilateral Suprarenalectomy for Hypersuprarenalism, *J. A. M. A.* **102** 1118 (April 7) 1934. DeCourcy, C., and DeCourcy, J. L. Essential Hypertension with Treatment by Bilateral Subtotal Adrenalectomy, *Am. J. Surg.* **25** 324, 1934. DeCourcy, J. L. Subtotal Bilateral Adrenalectomy for Hyperadrenalism (Essential Hypertension), *Ann. Surg.* **100** 310, 1934.

53 Adson, A. W., and Brown, G. E. Malignant Hypertension. Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the Sixth Thoracic to the Second Lumbar, Inclusive, *J. A. M. A.* **102** 1115 (April 7) 1934.

54 Craig, W. McK., and Brown, G. E. Unilateral and Bilateral Resection of the Major and Minor Splanchnic Nerves. Its Effects in Cases of Essential Hypertension, *Arch. Int. Med.* **54** 577 (Oct.) 1934.

55 (a) Shennan, T. Dissecting Aneurysms, Medical Research Council, Spec. Rep. Ser. 193, London, His Majesty's Stationery Office, 1934. (b) White, P. D., Badger, T. L., and Castleman, B. Dissecting Aortic Aneurysms Wrongly Diagnosed Coronary Thrombosis, *J. A. M. A.* **103** 1135 (Oct. 13) 1934. (c) Sponhalz, G. Idiopathischer Elasticaschwund und spontane Aortenrupturen, *Ztschr. f. Kreislaufforsch.* **26** 449, 1934.

Shennan found the incidence nearly twice as great among men as among women, and by far the greater number of cases occurred in the later decades of life. The most important determining factor is degeneration of the media, due in most cases to the selective action of toxins on the muscle fibers, followed by degeneration of the elastic and connective tissues. The proximate cause is an increase in arterial blood pressure due to physical effort or strong emotion. Syphilis is rarely an etiologic factor, in contradistinction to the common type of aortic aneurysm. The signs and symptoms may not be very distinctive. The one common feature is sudden onset, usually in a person who has previously shown no obvious symptoms of cardiovascular disease. There is usually a sense of anxiety and of something "giving away" in the chest, followed by intense pain in the thorax or abdomen. Pain may also be present in the side, back, head or limbs. Dyspnea, vomiting and dysphagia are less commonly present. Increase of cardiac dullness, dullness over one side of the thorax from fluid in the pleura and occasionally the absence or diminution of the pulse on one side were the most significant physical signs. The more general signs of cardiac disease and collapse gave little assistance. The duration of the illness is usually short, collapse and death frequently following the initial symptoms of an attack, while exceptionally excellent recovery is made. The author considers the main factor determining survival subsequent to the primary tear to lie in the varying period over which blood pressure is maintained at the height at which the primary rupture was produced.

White, Badger and Castleman<sup>56b</sup> call attention to 2 recent cases of dissecting aortic aneurysm (the diagnosis was incorrect in the first and correct in the second) with particular reference to the assembly of clues for differential diagnosis from coronary thrombosis. Such clues include (1) suddenness of onset of the maximal pain, (2) radiation of pain to the back and legs, (3) absence of marked hypotension, (4) absence of abnormal signs on cardiac auscultation and (5) a relatively normal electrocardiogram.

### VALVULAR HEART DISEASE

An important study has been made concerning the incidence and diagnosis of aortic stenosis<sup>56</sup>. At the Massachusetts General Hospital in 6,800 necropsies there were 123 (1.8 per cent) cases of aortic stenosis in contrast to 159 (2.3 per cent) cases of mitral stenosis in the same series. In another series of 4,800 patients with cardiovascular complaints the diagnosis of aortic stenosis was made in 113 cases (2.3 per cent). Calcareous valvular changes were found in 86 of the

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56 McGinn, S., and White, P. D. Clinical Observations on Aortic Stenosis, *Am J M Sc* 188 1, 1934

123 (70 per cent) cases that came to autopsy. In the group with calcareous changes the male sex predominated, and the patients were older. The most common etiologic factor was the rheumatic infection in youth, but there were many cases of uncertain origin. It was evident from this study that all grades of aortic stenosis exist, as in the case of mitral stenosis, that aortic stenosis even of considerable degree is common in New England, particularly in males, that calcareous changes are found chiefly in older patients, no matter what the cause, that aortic stenosis is sometimes associated with considerable hypertension, that the condition is often overlooked when it should be clinically diagnosed, that it may be suspected from the presence of a harsh aortic systolic murmur in a patient without syphilitic aortitis even in the absence of an aortic systolic thrill or a plateau pulse and in the presence of the aortic second sound, and, finally, that it is an important lesion to search for, even in the lesser grades, because of its progression and because of the frequency with which it is associated with congestive heart failure.

Twenty patients with mitral stenosis with attacks of acute pulmonary congestion with or without cardiac asthma have been studied<sup>57</sup> with particular reference to a comparison with a larger group (260 cases) with the more common type of acute pulmonary congestion without mitral stenosis but with obvious factors of strain acting on the left ventricle (systemic hypertension, aortic valvular disease, coronary thrombosis). In the small group of cases of uncomplicated mitral stenosis (10 cases) acute pulmonary congestion was observed in younger patients, the attacks were precipitated by exertion or by paroxysmal tachycardia and were often accompanied by frank hemoptysis. The prognosis is more favorable than in most other cases of cardiac asthma, although digitalis and diuretics are of less value. The best explanation of the acute pulmonary congestion here is that when the heart is stimulated to greater work the hypertrophied and dilated right ventricle propels more blood into the pulmonary vessels than can pass through the stenosed mitral valve in the same unit of time, with consequent acute pulmonary congestion.

### CORONARY HEART DISEASE

*Angina Pectoris*—Gallavardin<sup>58</sup> places insistence on the recognition of angina pectoris in two fundamental forms: syphilitic angina pectoris and arteriosclerotic angina pectoris. The same clinical syndrome covers these two varieties, which are distinct in their etiology,

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<sup>57</sup> McGinn, S., and White, P. D. Acute Pulmonary Congestion and Cardiac Asthma in Patients with Mitral Stenosis, *Am Heart J* 9: 697, 1934.

<sup>58</sup> Gallavardin, A. Les deux angines de poitrine coronariennes, *Médecine* 15: 185, 1934.

lesions, treatment, clinical course and prognosis. He discusses the differential diagnosis, which is rather easy in the majority of the cases but may exceptionally present great difficulties, as in aged patients with a proved syphilitic condition.

It has been experimentally shown that pain may arise in contracting somatic muscle deprived of its blood supply. The analogy of pain arising in the cardiac muscle followed this logically and was proved in studies on the angina of effort.<sup>59</sup> The old theory that anginal pain arises from relative ischemia was established as fact and rival theories were destroyed. Further objective studies on the angina of effort have been made,<sup>60</sup> to ascertain by actual test the relationship of the pain to such factors as the taking of exercise, gastric distention, external temperature and repeated effort. The most interesting observation was that two types of angina of effort exist. In both, tolerance for exercise is constant if sufficient rest is allowed between the end of one attack and the start of the next test. In one type, as this period of rest is reduced, tolerance for exercise gradually diminishes, in the other type there is a phase which may be as long as an hour, during which tolerance for exercise is increased. Tolerance for exercise was found to be reduced an average of 25 per cent after a heavy meal. Distention of the stomach with air, however, did not affect tolerance for exercise, and it was concluded that the effect after the ingestion of food was occasioned by the increased expenditure of energy of the heart. Variations in external temperature did not appreciably affect tolerance for exercise in cases of angina of effort in which tests were made, although there is much clinical evidence to the contrary.

If patients suffering from angina pectoris breathe air deficient in oxygen pain may arise as the result of anoxemia. The clinical counterpart of this experiment is seen in certain patients with severe anemia who suffer anginal attacks. Hochrein and Matthes<sup>61</sup> found the relationship between anemia and angina to be extremely slight, among 297 patients with angina only 5 had severe anemia and 3 of these had coronary heart disease. Pickering and Wayne<sup>62</sup> reported observations on a series of 25 patients with anemia, 8 of whom complained of pain

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59 Wayne, E. J., and La Place, L. Observations on Angina of Effort, *Clin Sc* **1** 103, 1933.

60 Riseman, J. E. F., and Stern, B. A Standardized Exercise Tolerance Test for Patients with Angina Pectoris on Exertion, *Am J M Sc* **188** 646, 1934.  
Wayne, E. J., and Graybiel, A. Observations on the Effect of Food, External Temperature and Repeated Exercise on Angina of Effort, with a Note on Angina Sine Dolore, *Clin Sc* **1** 287, 1934.

61 Hochrein, M., and Matthes, K. Anemia and Angina Pectoris, *Deutsches Arch f klin Med* **177** 1, 1934.

62 Pickering, G. W., and Wayne, E. J. Observations on Angina Pectoris and Intermittent Claudication in Anemia, *Clin Sc* **1** 305, 1934.

over the sternum induced only by exercise and relieved by rest, in 6 this pain was no longer experienced after the anemia had been cured, while in 2 it persisted. The authors conclude from their experiments that the essential factor in the production of anginal pain in anemic patients is a diminished supply of oxygen to the working cardiac muscle and not an inadequate flow of blood.

The relationship of the use of tobacco and alcohol to angina pectoris has long been a subject of much practical interest, but it has never progressed much beyond the limits of medical gossip and hearsay. To aid in the problem a study<sup>63</sup> has been made of the past habits in the use of tobacco and alcohol of 750 consecutive patients with angina, controlled by the study of similar habits in 750 patients without angina with the same sex and age distribution and from the same walks of life. Comparison of the two groups showed that 46 per cent of the patients with angina had been abstainers from tobacco while 24 per cent had used tobacco to excess, in contrast to 37 per cent of the control series who did not smoke and 34 per cent who smoked excessively. Total abstention from alcohol was the history of 62 per cent of the control series. Only 8 of the 750 patients with angina drank considerable or excessive amounts of alcohol, while 63 of the control series drank much alcohol. It appears from this study that neither the use of, nor the abstention from, tobacco or alcohol plays an important rôle in the genesis of angina pectoris. In occasional cases the use of tobacco apparently aggravates or precipitates attacks of angina pectoris, and in occasional cases alcohol helps to prevent or relieve such attacks.

Complete removal of the thyroid gland in appropriate cases of angina pectoris has been established as a valuable procedure. Criteria for the proper selection of patients cannot be given categorically, the problem is more individual. It may be stated in general terms, however, that this operation may be considered for patients for whom medical treatment is unsatisfactory if a sufficient lowering of the basal metabolic rate can be expected and if the patient's fitness for operation can be proved.

The mechanism of the relief of anginal pain following total thyroidectomy has been considered. Weinstein and his associates<sup>64</sup> not infrequently found that the pain in the chest disappeared shortly after operation, before the basal metabolic rate had been changed. They give good evidence that this is related to the interruption of afferent nerve

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<sup>63</sup> White, P. D., and Sharber, T. Tobacco, Alcohol and Angina Pectoris, *J. A. M. A.* **102** 655 (March 3) 1934.

<sup>64</sup> Weinstein, A. A., Davis, D., Berlin, D. D., and Blumgart, H. L. The Mechanism of the Early Relief of Pain in Patients with Angina Pectoris and Congestive Failure After Total Ablation of the Normal Thyroid Gland, *Am. J. M. Sc.* **187** 753, 1934.



impulses from the heart. This improvement is temporary, however, the permanent relief is concomitant with the lowering of the basal metabolic rate. Horgan and Lyon<sup>65</sup> report that division and ligation of both superior and inferior thyroid arteries has relieved patients of anginal attacks and has permitted them to lead relatively active lives. Following thyroidectomy in the dog, Shambaugh and Cutler<sup>66</sup> found no demonstrable change in response produced by occlusion of the left descending coronary artery. The sensory pathways of the heart are presumably left intact. They believe that the beneficial effect of removal of the thyroid gland in angina pectoris may be due, in part at least, to a diminished effectiveness of the physiologic output of epinephrine.

A number of reports have appeared concerning the value of certain xanthine compounds and extracts of tissue as coronary dilators. A long-sustained increase in coronary circulation has not been shown in experiments on animals, and conclusions based on clinical studies are reached with great difficulty. At present we are not convinced that any of these preparations have great value.

*Cardiac Infarction*—Studies relating to electrocardiographic diagnosis and localization of cardiac infarction have been mentioned under the section on electrocardiography. The value of oxygen therapy will be discussed in the next section.

## CONGESTIVE HEART FAILURE AND ITS TREATMENT

The difficulties and complexities attending the explanation of the nature of congestive heart failure are shown in the reports by the Harrisons and their associates, which now number over twenty articles. In recent studies<sup>67</sup> they have investigated chiefly certain respiratory

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65 Horgan, E., and Lyon, J. A. Division and Ligation of Superior and Inferior Thyroid Arteries in Treatment of Angina Pectoris. Report of Case, *M. Ann. District of Columbia* **3** 123, 1934. Lyon, J. A., and Horgan, E. Dissociation of Thyroid from Sympathetic Nervous System and Reduction of Blood Supply to Thyroid in Angina Pectoris, *South M. J.* **27** 985, 1934.

66 Shambaugh, P., and Cutler, E. C. Total Thyroidectomy in Angina Pectoris. An Experimental Study, *Am. Heart J.* **10** 221, 1934.

67 Harrison, T. R., Friedman, B., Clark, G., and Resnik, H. The Cardiac Output in Relation to Cardiac Failure, *Arch. Int. Med.* **54** 239 (Aug.) 1934. Harrison, W. G., Jr., Calhoun, J. A., and Harrison, T. R. Congestive Heart Failure. XVIII. Clinical Types of Nocturnal Dyspnea, *ibid.* **53** 56 (April) 1934. Harrison, W. G., Jr., Calhoun, J. A., Marsh, J. P., and Harrison, T. R. Congestive Heart Failure. XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, *ibid.* **53** 724 (May) 1934. Harrison, T. R., King, C. E., Calhoun, J. A., and Harrison, W. G., Jr. Congestive Heart Failure. XX. Cheyne-Stokes Respiration as the Cause of Paroxysmal Dyspnea at the Onset of Sleep, *ibid.* **53** 891 (June) 1934. Harrison, T. R., Calhoun, J. A., and Harrison, W. G., Jr. Congestive Heart Failure. XXI. Observations Concerning the Mechanism of Cardiac Asthma, *ibid.* **53** 911 (June) 1934.

difficulties in relation to congestive failure. They have found that while the cardiac output of patients with congestive failure is usually from 10 to 30 per cent less than that of normal subjects the output may be within the normal range. The average values are similar for patients with compensation and with decompensation and in a given patient clinical improvement and disappearance of congestive failure may be associated with an increase, a decrease or no change in this function. These workers interpret these observations as favoring the "backward failure" theory of heart failure. They believe that the fundamental cause of nocturnal dyspnea is an increase in the degree of pulmonary congestion consequent to "back failure" from the left side of the heart. The vagus fibers are very sensitive to pulmonary congestion, and this leads to a reflex stimulation of breathing. Changes in the oxygen, carbon dioxide or acid-base equilibrium in arterial blood were not found to be important in initiating dyspneic attacks. Coughing, previous activity, overeating and dreams were listed as precipitating factors. They describe four types of nocturnal dyspnea occurring in cardiac disease, these are orthopnea, evening dyspnea, Cheyne-Stokes respiration and cardiac asthma.

Cohn and Steele<sup>68</sup> have shown that the elevation of temperature in heart failure need not be of infectious origin but may depend on a variety of processes incident to the failure. In certain patients with heart failure who exhibit fever, not only was evidence of infection sought in vain but the behavior of the skin temperature of the extremities differed from that in patients with fever associated with infectious disease. In patients with heart failure the skin temperature is lower than that of normal persons, while that of patients with infectious fever is as high as, or higher than, normal.

It is not possible properly to evaluate the treatment of congestive failure by complete removal of the thyroid gland. A report on 50 patients so treated in the course of eighteen months has been made by Blumgart and his associates,<sup>69</sup> to which the reader is referred for details concerning their method of procedure. It has been shown that congestive heart failure can be abolished in at least half the patients operated on, and unquestionably most of these patients showed considerable subjective improvement. However, this does not decide the matter. It must be shown that the improvement is sufficiently long lasting. A major procedure like total thyroidectomy must promise

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68 Cohn, A. E., and Steele, J. M. Unexplained Fever in Heart Failure, *J. Clin. Investigation* **13** 853, 1934.

69 Blumgart, H. L., Berlin, D. D., Davis, D., and Riseman, J. E. F. Total Ablation of Thyroid in Angina Pectoris and Congestive Failure. XI. Summary of Results in Treating Seventy-Five Patients During the Last Eighteen Months, *J. A. M. A.* **104** 17 (Jan. 5) 1935.

a comparatively great reward. Even if this operation is successful it must be remembered that the patient faces congestive failure again in a relatively short time with the reexperiencing of previous events. This involves a consideration not only of the patient's wishes but of far-reaching social and economic factors of which the patient is often the poorest judge.

Recent studies<sup>70</sup> have emphasized the value of oxygen therapy in cases of heart failure. It has been shown that a majority of patients with cardiac failure of the anginal or congestive type are improved after being kept in an atmosphere of from 40 to 50 per cent oxygen for long periods. The clinical indications for oxygen therapy in relative order of importance are dyspnea, restlessness, anginal pain, cyanosis and cough. In order to provide adequate concentration the oxygen tent or chamber is to be preferred to administration by nasal catheter, but the latter is much less expensive, treatment should be continuous over a period of days. In favorable cases of congestive failure the response follows a fairly definite pattern, dyspnea and restlessness are partly relieved in a few hours but are completely relieved only after several days, arterial oxygen is restored to normal, a gradual rise in the carbon dioxide content of the blood occurs, and increase in urinary chloride and excretion of water may lead to a complete loss of edema.

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70 Richards, D. W., Jr., and Barach, A. L. Prolonged Residence in High Oxygen Atmospheres. Effects on Normal Individuals and on Patients with Chronic Cardiac and Pulmonary Insufficiency, *Quart J Med* **3** 437, 1934. Barach, A. L. Analysis of Three Hundred and Seventy-Six Consecutive Oxygen-Treated Cases from a Study Made at the Presbyterian Hospital, New York, from 1929 to 1932, *New York State J Med* **34** 41, 1934, The Treatment of Asphyxia in Clinical Disease, with Especial Reference to Recent Developments in the Use of Oxygen in Heart Disease, *ibid* **34** 672, 1934.

## Book Reviews

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**Studies on Alimentary Lipaemia in Man** By N I Nissen Pp 176 Copenhagen Levin & Munksgaard, 1933

In this thesis for the doctorate of medicine at the University of Copenhagen the author reviews a difficult subject, namely, that of blood lipids and fat tolerance. The thesis is published in English, the translation is passable.

The matter of blood lipids is confusing because of the well established fact that all the fats and lipoids of the blood are difficult to extract by means of the ordinary solvents of fat. Thus, different methods yield more or less of the various fractions, phospholipoids, cholesterol esters, free cholesterol and neutral fat. Nissen, in his investigation, limited his attention to the primary ethereal extract of dried blood. This, he says, contains all the neutral fat of the blood, together with the main part of the free cholesterol, little or no phosphorus to indicate the presence of any phospholipoid and no cholesterol esters. The micromethod of extraction of 0.1 cc of dried blood is that described by Bing and Heckler, under whose direct supervision Nissen's study was conducted.

The observations reveal that the free cholesterol concentration of the blood in man does not change in alimentary lipemia, and that variations in the primary ethereal extract which follow meals of fat are attributable exclusively to neutral fat. The average value for blood taken when the subject is fasting is 64.6 mg per hundred cubic millimeters, which agrees well with the findings of others. During fasting the values for a given person are rather constant from day to day. After an intake of 1 Gm of fat per kilogram of body weight a rise occurs, amounting in normal persons (forty-eight subjects) to from 15 to 100 per cent of the value during fasting, with an average of 41 per cent. The height of the curve is somewhat but not entirely dependent on the amount of fat fed. The highest increase—183 per cent—was obtained after feeding 3 Gm of fat per kilogram of body weight, that obtained after feeding 6.4 Gm per kilogram was only 162 per cent. Similar results were obtained in other experiments on children. Analyses of the feces indicated almost complete absorption, even with the very large doses of fat, thus the differences observed could not be accounted for by differences in absorption.

The administration of a second dose of fat from two to four hours after a primary dose did not cause a further increase in lipemia. This was taken to mean that the capacity of the organism to remove fat from the blood stream is increased by feeding fat. Dextrose administered, either by mouth or by vein, together with a dose of fat, depressed the alimentary lipemia as long as any hyperglycemia persisted, later, after the blood sugar had fallen to normal, the blood fat rose as high as, or higher than, it would have risen had the fat been given alone. In other words, the lipemic reaction to the fat was not prevented by carbohydrate, but simply delayed. On the other hand, the ingestion of fat together with dextrose did not influence the course of the hyperglycemia attributable to the dextrose. No explanations are offered for these observations, as the questions require further investigation before they can be answered.

Various pathologic abnormalities were then investigated. Among eleven diabetic patients, in ten of whom the disease was in an uncontrolled stage, Nissen found normal values during fasting in all but two and no alimentary hyperlipemia in all but four. In no case was the value during fasting higher than normal, or the peak of the alimentary lipemia more than 150 mg per hundred cubic millimeters, except in cases in which the condition was complicated by arteriosclerosis. Two of the patients were young, both of these showed normal curves for blood fat. Nissen concludes that the diabetic disturbance of carbohydrate metabolism has little influence on the assimilation of alimentary fats.

The same is true in obese subjects. The findings in the subjects studied indicated that corpulence was not associated with any decrease in fat tolerance. On the other hand, three of six patients with arteriosclerosis showed distinctly abnormal curves for blood fat, with increases ranging from 140 to 243 per cent. Two others showed

minor variations. High values for blood fat were also found in patients with nephrotic conditions, as was to be expected.

The studies of Dr. Nissen deserve careful consideration by those interested in the part played by lipemia in arteriosclerosis. To the reviewer, and contrary to an opinion very current today, they suggest the conclusion that lipemia is not a cause but rather a result of arteriosclerosis.

**Practical Endocrinology** By Max Goldzieher, M.D. Price, \$5 Pp 326, with 41 illustrations. New York: D. Appleton-Century Company, Inc., 1935.

This book is designed to approach the endocrinopathies as the practitioner meets them. One is therefore not presented with a list of glandular disturbances and the usual descriptions of the etiology, symptomatology and diagnosis, but is led from the presenting manifestations to the incrimination of the involved gland by a differential diagnosis of important symptoms. Of thirty-eight chapters, the first two deal very briefly with the embryology, anatomy, histology and physiology. A chapter on the examination of the patient is included and covers the essential factors in the history and physical examination. Laboratory procedures are discussed, including the basal metabolic rate, analysis of the blood, dextrose, fat and salt tolerance tests, and hormone and pharmacologic tests. Chapters 4 to 28 deal with endocrine disturbances arranged, as has been previously stated, in a symptomatic and systemic approach. Chapters 28 to 38 describe therapeutic procedures considered briefly and concisely.

Goldzieher, for the sake of brevity, eliminates much controversial material and presents his personal concepts as definite points of view, whether or not these have been universally accepted. There are no references. Some considerations, for example, the discussion of parathyroid function, are extremely superficial. In the discussion and classification of obesity the vague description of the fundamental concept of obesity leaves the reader confused in regard to the author's views, and one seriously doubts his adherence to the law of the conservation of energy. In general, however, the discussions are clear and adequate for a work of this type.

The reviewer considers the author's approach to the endocrine disorders a valuable one but must admonish the reader that in a field beset with much controversy and theory the opinions of one man, given to the exclusion of others, should be read with a critical eye.

**Food and Health** By Henry C. Sherman. Price, \$2.50 Pp 296. New York: The Macmillan Company, 1934.

Every one is familiar with Dr. Sherman's valuable original work on problems of nutrition and with his book on the vitamins. The present volume, it appears, is written for the general reader rather than the specialist. While no one can quarrel with the validity of most of the facts, Sherman has unfortunately fallen into that distemper so common with the specialist when presenting his subject to the laity of overemphasizing small points in such a way as to create confusion and alarm in the minds of the readers. The average business man or housewife after studying this book will believe that physical dissolution is at hand unless one begins to live one's life around vitamins, counted calories and balanced rations of salt. Sherman seems to lose sight of the fact that it is only the occasional *specially* susceptible person who shows clinical evidences of nutritional deficiency on any ordinary sort of diet, even a poor one, the ration must be grotesquely scanty or ill-balanced before anything approaching large numbers will be affected. In brief, the whole thesis is overdone. One needs to proceed no further than page 2 to find the unproved (for man) statement that "a merely ill-chosen or poorly-balanced food supply may diminish our ability to resist infections", and so it goes throughout the book. Finally there is appended a record of the daily diet over a period of months planned in accordance with the "principles which this book seeks to explain." These meals seem about like those which any ordinary person eats, although some of them are not too inviting. The following is an example: lunch—pea soup, whole wheat wafers, pear and cream cheese salad, raisin bread and milk.

## CARDIOVASCULAR SYPHILIS

EARLY DIAGNOSIS AND CLINICAL COURSE OF AORTITIS IN THREE  
HUNDRED AND FORTY-SIX CASES OF SYPHILIS

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In the hope of adding to the current knowledge of some of the little understood phases of cardiovascular syphilis, a study was begun in 1927 in the clinics for adults with cardiac disease and syphilis of the Brooklyn Hospital. The plan of the study was as follows. Every patient in the clinic for syphilis who would consent was referred to the clinic for cardiac disease for complete cardiovascular examination. This included taking a history and making a physical examination.<sup>1</sup> Electrocardiograms and teleroentgenograms were taken, and Wassermann tests of the blood were made for nearly every patient. Of more importance, however, is the fact that these patients have been and, it is hoped, will be examined regularly in the clinic for cardiac disease at least every six months. The present paper is a preliminary report, giving an analysis of the facts observed in the first five years of the study.

Some of the major aims of the study are to attempt to describe the course of this disease, to discover in how many patients aortitis develops and what effect treatment has in preventing the development of this complication or in relieving symptoms or prolonging life. In this report we are primarily interested in the early diagnosis of aortitis.

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This paper is no. 10 in the series "Statistical Studies Bearing on Problems in the Classification of Heart Diseases."

From the Department of Medicine and the Cardiac Clinic of the Brooklyn Hospital and the Heart Committee of the New York Tuberculosis and Health Association.

Read at a meeting of the Committee on Cardiac Clinics of the New York Tuberculosis and Health Association at the New York Academy of Medicine, Dec 9, 1932.

<sup>1</sup> The standard charts prepared by the research subdivision of the Heart Committee of the New York Tuberculosis and Health Association were used.

The patients come to the clinic for syphilis for treatment on their own motion or are referred by other departments of the hospital. They may be in the primary, secondary or tertiary stages and are referred to the clinic for cardiac disease regardless of whether they have cardiovascular lesions.

In the selection of cases certain definite criteria were established. In the first place, proof of the presence of syphilis beyond reasonable doubt was required. In order to establish a diagnosis of syphilis a history of chancre and one reliable, strongly positive Wassermann reaction were necessary, or, in the absence of a history of primary infection, at least two strongly positive Wassermann reactions. In those cases in which neither a positive history nor a positive Wassermann reaction was obtained, indisputable evidence of syphilis other than of the cardiovascular system, such as *tabes dorsalis* or *dementia paralytica*, was regarded as essential.

Next came the much more difficult problem of establishing criteria for the diagnosis of aortitis uncomplicated by aortic insufficiency or aortic aneurysm. We were aware of the existence of a considerable body of competent opinion which holds that, in the absence of aneurysm or gross abnormality of the aorta, it is not safe to make a positive diagnosis of syphilitic aortitis before the appearance of aortic insufficiency.<sup>2</sup> We were familiar, furthermore, with the appearance of the aorta in roentgenograms and with the fluoroscope in syphilitic aortitis.<sup>3</sup> Since a considerable number of persons were included in the study in whom the syphilitic infection was of short duration and in whom the usual clinical symptoms and physical signs that confirm a diagnosis of aortitis would probably be absent, we found it necessary to establish criteria which would enable us to state whether the aorta was enlarged. Except in a few early cases, at least one roentgenogram<sup>4</sup> of the heart and aorta of every patient was taken at a distance of 2 meters, in the usual postero-anterior position and also in the left anterior-oblique view. This examination was supplemented by a fluoroscopic one in many instances. The width of the aortic shadow was measured in the postero-anterior view by the method of Vaquez and Bordet,<sup>5</sup> that is to say, by adding the measurement of the farthest point on the ascending aorta to the right of the midsternal line to the measurement of the farthest point of the aortic knob to the left of the midsternal line. The sum

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2 Conner, L. A., in discussion on Steel.<sup>3</sup>

3 Steel, D. The Roentgenological Diagnosis of Syphilitic Aortitis, Review of Forty Proved Cases, *Am Heart J* 6 59, 1930.

4 Dr. Ruth Ingraham, roentgenologist of the Brooklyn Hospital, made and interpreted the roentgen measurements.

5 Vaquez, H., and Bordet, E. *The Heart and the Aorta*, New Haven, Conn., Yale University Press, 1920.

gives a figure which represents the total width of the shadow comprising the aortic arch and does not include the shadow of the descending aorta. For brevity, this measurement will be referred to as the "width of the aorta" although it is realized that it is in no way descriptive of the true diameter of the aorta. It is not possible to ascertain the latter measurement, especially in young subjects.

To find limits for the width of the normal aortic silhouette proved to be a difficult task, because it is probable that the total transverse diameter varies considerably. Reliance was placed, therefore, on the description of the contour of the ascending aorta and arch, special attention being given to bulging of the ascending aorta as seen in the teleroentgenograms or with the fluoroscope. Bainton's<sup>6</sup> work on the normal aortic silhouette was useful. He found in normal male and female subjects from the second through the sixth decade that up to the age of 50 the extreme variation of the normal aortic silhouette was between 4 and 6.7 cm for males and between 3.8 and 6.2 cm for females. Through the age of 59 the highest normal figure was 7 cm. In the present study all aortic measurements of less than 6 cm were considered normal. In all instances in which the aorta measured between 6 and 7 cm the films were restudied, or if they were not available the written descriptions and fluoroscopic reports were reviewed. All instances in which the widening of the aortic shadow might be due to a high level of the diaphragm, improper centering of the patient or scoliosis were excluded. The others were carefully studied especially for the presence or absence of bulging of the ascending aorta. When bulging was found those aortas measuring between 6 and 7 cm were considered abnormal. All aortas measuring 7 cm or more were classified as dilated.

In order to make a diagnosis of syphilitic aortitis in the absence of aortic insufficiency or aneurysm it is necessary not only to demonstrate bulging or enlargement of the aorta but to recognize other clinical conditions in which the aorta is dilated, these are arterial hypertension, arteriosclerosis and aortic regurgitation of rheumatic origin. Cases of arterial hypertension have been excluded by limiting the group of patients with simple aortitis to those with a systolic blood pressure of less than 140 mm of mercury. There was only one exception to this rule in the case of a patient whose systolic pressure ranged between 140 and 150. Cases of arteriosclerosis were excluded by limiting the group to patients under 50 years of age. Patients presenting evidence of peripheral arteriosclerosis were placed in a group subsequently referred to as that with aortitis or arteriosclerosis. In order to exclude the

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<sup>6</sup> Bainton, J. H. The Silhouette of the Heart and the Aortic Arch, *Am Heart J* 6:616, 1933.



effect of acute rheumatic infection or dilatation of the aorta, no patient with a history of the diseases included in the rheumatic state was admitted. Pappenheimer and Von Glahn<sup>7</sup> have described lesions of rheumatic fever in the aorta in 2 patients and called the condition rheumatic aortitis. It is not known whether the aorta is dilated in this disease, but it is certain that aortic regurgitation of rheumatic origin causes considerable pulsation of the aorta, which is visible with the fluoroscope. Such cases have been excluded.

To recapitulate, all our patients with simple aortitis are known to have been syphilitic. None has been subject to rheumatic fever or arterial hypertension. None is over 49 years old or presents any evidence of peripheral arteriosclerosis. When the aorta is dilated it is highly probable, therefore, that syphilis is the cause of the dilatation and that a clinical diagnosis of syphilitic aortitis is justified.

One of the aims of this study, as has been mentioned, is to try to discover a method by which the diagnosis of syphilitic aortitis can be made much earlier than in the past. By the time the aortic second sound has become hollow and accentuated, a systolic murmur has appeared at the aortic area or symptoms such as paroxysmal dyspnea or substernal pain have developed, the syphilitic process in the aorta is well advanced. We have turned to the x-ray film and fluoroscopy to discover whether these methods can throw further light on the possibility of early detection.

#### MATERIAL

*Incidence*—Three hundred and forty-six patients who satisfied the criteria just described were studied. Syphilis was of the acquired type except in 14 patients (4 per cent), in whom it was congenital. Less than half (41.9 per cent) presented evidence of cardiovascular syphilis. This is a higher incidence than has been reported by other observers. Turner<sup>8</sup> found an incidence of 10.1 per cent in 6,420 patients in the late stages of syphilis. What the percentage of patients infected with syphilis who show involvement of the cardiovascular system ultimately might be may be learned from a study of autopsies. Langer<sup>9</sup> maintained that from 70 to 80 per cent of all syphilitic patients among 23,105 who came to necropsy at the Rudolf Virchow Krankenhaus presented evidence of involvement of the aorta. Moore, Dangle and

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7 Pappenheimer, A. M., and Von Glahn, W. C. A Case of Rheumatic Aortitis with Early Lesions in the Media, *Am J Path* **2** 15, 1926, *Studies in the Pathology of Rheumatic Fever*, *ibid* **3** 583, 1927.

8 Turner, T. B. The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, *Bull Johns Hopkins Hosp* **46** 159, 1930.

9 Langer, E. Die Häufigkeit derluetischen Organveränderungen insbesondere der Aortitis luetica, *München med Wchnschr* **73** 1782, 1926.

Reisinger<sup>10</sup> placed the figure based on evidence collected in this country and abroad at between 80 and 90 per cent

*Sex*—The preponderance of males with syphilis, as compared with females (a proportion of approximately 2:1), is in agreement with other observations (table 1). Lamb and Turner<sup>11</sup> found it to be 3:1.

*Race*—Since this study was made in a northern community where the number of Negroes is small, the white race was found to make up a large percentage of the cases (white race, 81 per cent, and colored race, 19 per cent). The incidence of cardiovascular syphilis was only slightly higher among the colored race (45.5 per cent), as compared with 41.8 per cent among the white patients. Turner<sup>8</sup> found a somewhat higher ratio of colored patients to white patients in a southern population—114:72 per cent. About one third of the white patients were females, while approximately one half (48.5 per cent) of the Negro patients were females.

TABLE 1—Incidence of Syphilis According to Sex

	Both Sexes		Males		Females	
	Num ber	Per centage	Num ber	Per centage	Num ber	Per centage
Evidence of cardiovascular syphilis	145	100	101	69	44	31
No evidence of cardiovascular syphilis	201	100	119	59	82	41
Total number of cases	346	100	220	64	126	36

*Age at Occurrence of Primary Lesion*—Syphilis is usually acquired in late adolescence and early adult life. In 190 patients (55 per cent) the date of the occurrence of the primary lesion was known. One fourth of our patients acquired syphilis before the age of 21, one-half before the age of 25, and three-fourths before the age of 30 (fig. 1).

*Interval from Occurrence of Primary Lesion to First Observation in Clinic for Cardiac Diseases*—In order to describe the natural history of cardiovascular syphilis it is necessary to know the age at which infection occurred. Half of our patients were examined within ten years of the time after the primary lesion was acquired, but the average period for the whole group was thirteen years. It is noteworthy that 25 per cent were examined within one year after the occurrence of the initial lesion, owing to the fact that the clinic for syphilis referred cases promptly (fig. 2).

10 Moore, J. E., Danglade, J. H., and Reisinger, J. D. Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm, *Arch. Int. Med.* 49:766 (May) 1932.

11 Lamb, A. R., and Turner, K. B. Cardiovascular Syphilis in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1932, vol. 4, chap. 3, p. 337.

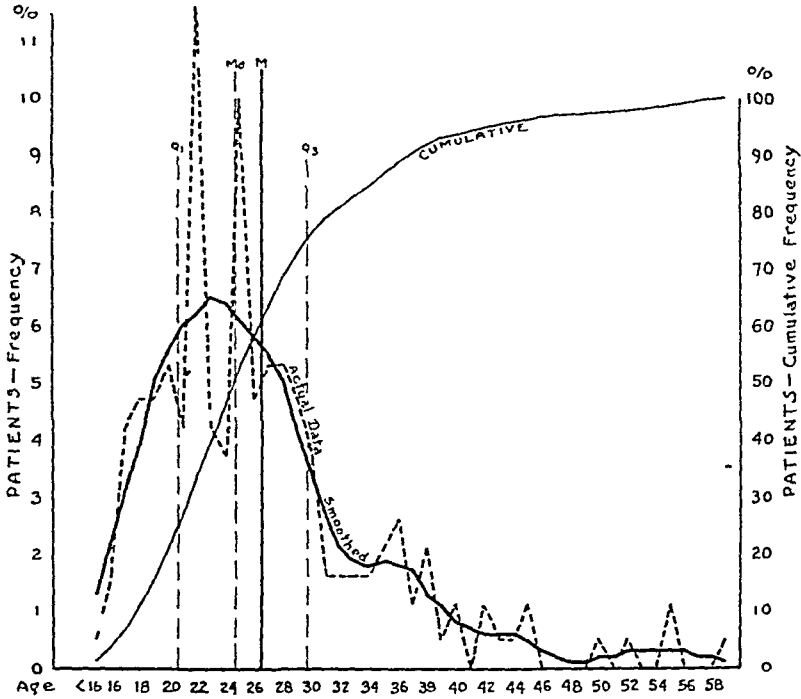


Fig 1—Age at the occurrence of the primary lesion In this figure and in figures 2, 3 and 4,  $Q1$  indicates the data for one fourth of the patients,  $Q3$ , for three fourths,  $Md$ , for one half, and  $M$ , for the average number

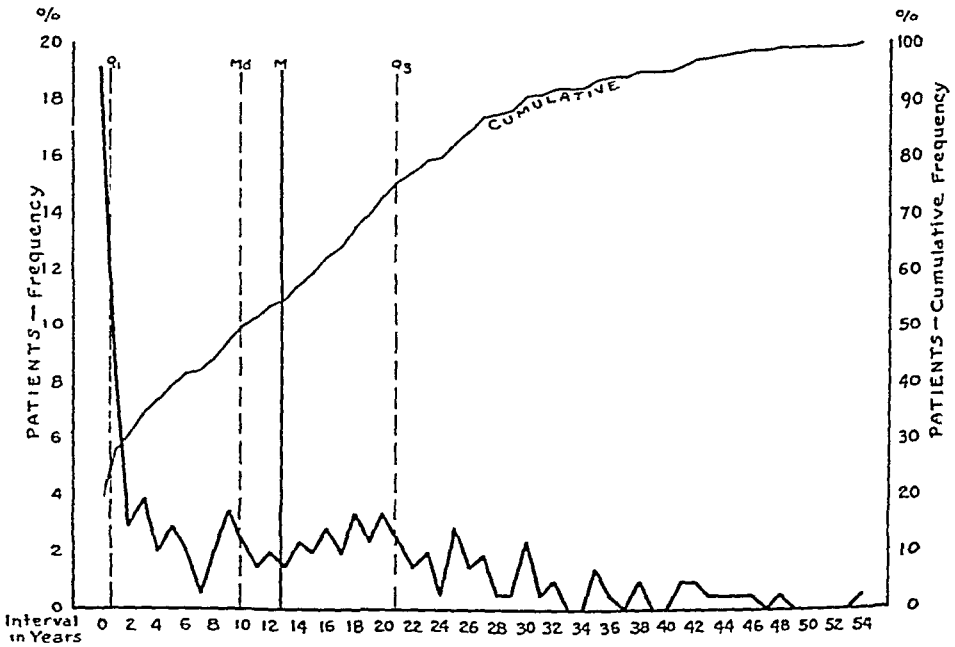


Fig 2—Interval from the occurrence of the primary lesion to the beginning of observation in the clinic for cardiac diseases

*Interval from Occurrence of Primary Lesion to Discovery of Cardiovascular Syphilis*—It has frequently been reported that the “latent” period, that is to say, the interval between the occurrence of the initial lesion and the onset of symptoms and physical signs of cardiovascular disease, is long, usually from sixteen to twenty years. DeGraff,<sup>12</sup> in an analysis of the records of about 200 deceased patients who had been treated for cardiovascular syphilis in Bellevue Hospital, found that the average interval from infection to the discovery of heart disease was twenty-two and seven-tenths years. He found, further, that more than two thirds had applied for treatment in the clinic for cardiac disease within two years after the symptoms were first experienced and that

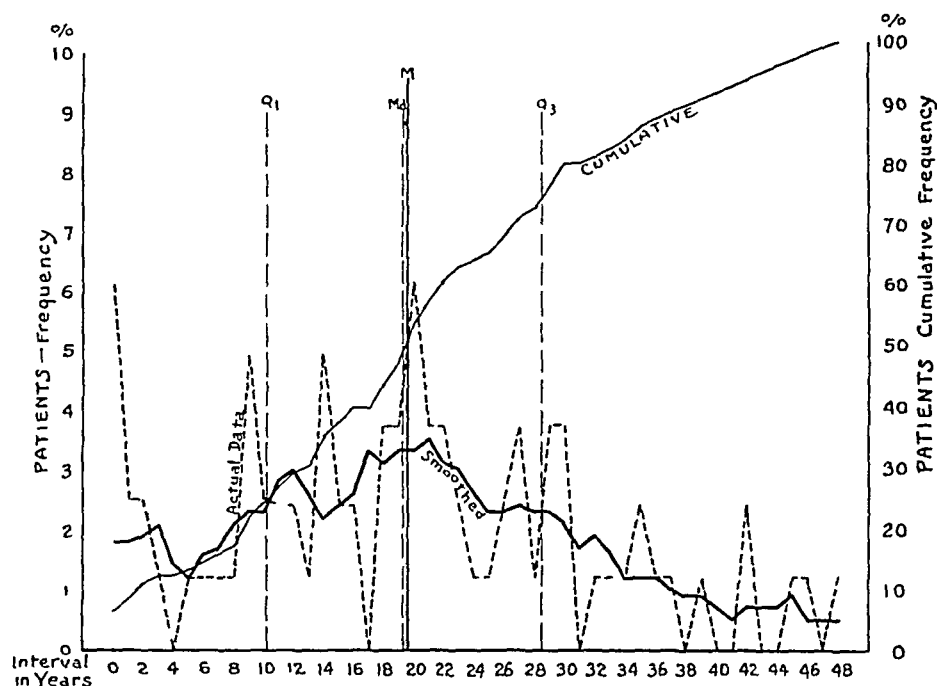


Fig 3—Interval between the occurrence of the primary lesion and the discovery of cardiovascular syphilis

a diagnosis of heart disease was made simultaneously with the first complaint in more than half. In only 10 per cent was the interval from infection to the discovery of heart disease less than ten years.

In our group, which, as has been pointed out, came under observation in the clinic for cardiac disease earlier after the initial infection than is customarily the case, one fourth showed evidence of cardiovascular syphilis within ten years after the occurrence of a chancre (fig 3), although the mean interval was twenty years. Discovery of cardiovascular involvement must not be taken to indicate the time at which the heart becomes infected. At present involvement can be recognized only after gross changes have taken place in the aorta.

12 Personal communication to the authors

*Interval from Occurrence of Primary Lesion to Onset of Cardiac Symptoms*—The next milestone in the course of cardiovascular syphilis is the point at which the damage has become great enough to cause symptoms. Under cardiac symptoms are included palpitation, precordial pain and dyspnea. These symptoms, in the form of sudden onset of circulatory embarrassment and paroxysmal dyspnea, are not believed to be characteristic of aortitis. Since we were trying to discover means for the earliest possible recognition of cardiovascular syphilis, it seemed desirable to include any symptoms that might direct attention to the heart. Almost half of the patients (49 per cent) who presented cardiovascular syphilis complained of symptoms. These began, on the average, twenty years after infection (fig 4).

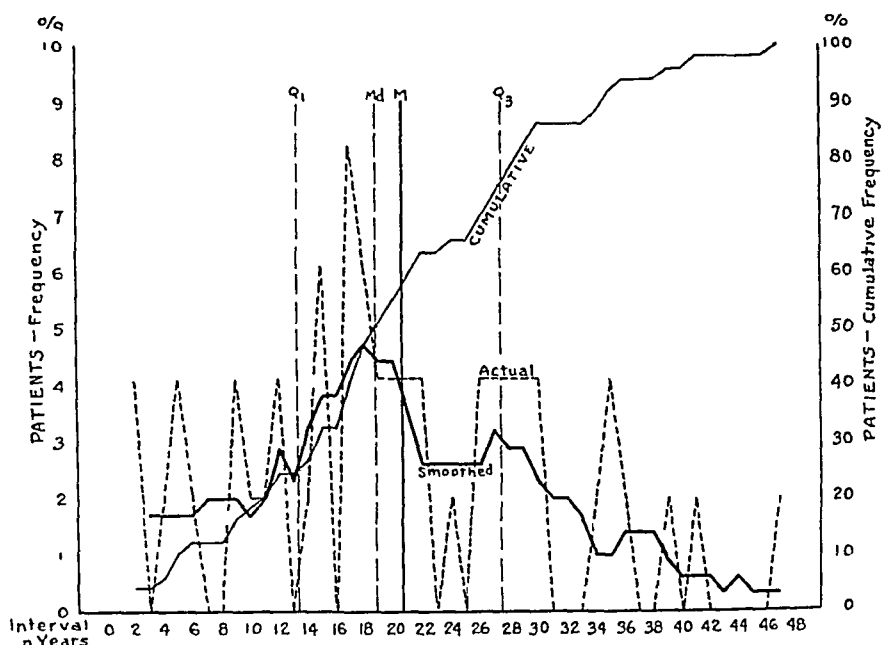


Fig 4—Interval between the occurrence of the primary lesion and the onset of cardiac symptoms

The mean interval from the occurrence of the primary lesion to the discovery of heart disease and that from the occurrence of the lesion to the onset of symptoms therefore coincide. In our experience symptoms were conspicuous by their absence in the early cases and were not helpful in the early diagnosis of aortitis. Of 59 patients with uncomplicated aortitis, 13 (22 per cent) presented symptoms referable to the heart. In these patients aortic insufficiency, aneurysm or disease of the coronary arteries had not developed.

*Etiologic and Anatomic Diagnosis*—In any study of the course of cardiovascular syphilis it is important to separate patients suffering from syphilis alone from those suffering also from arteriosclerosis, for example

In 93 patients syphilis alone was the etiologic factor. Patients over 50 years of age, as well as those who had a history of rheumatic disease or clinical evidence of arteriosclerosis or arterial hypertension, were, as has been stated, excluded. There were, in addition, 7 cases of cardiovascular syphilis complicated by heart disease clearly due to arterial hypertension or to rheumatic fever. In another, larger group of patients either 50 years old or suffering from peripheral arteriosclerosis, it was impossible to be certain whether widening of the aorta was due to syphilis or arteriosclerosis. These cases, which numbered 45, were designated as cases of syphilis or arteriosclerosis (table 2). The high percentage of cases of uncomplicated aortitis (40.6) in which syphilis alone was the etiologic factor is striking. Fifteen per cent of the

TABLE 2—*Anatomic Diagnosis*

Anatomic Diagnosis	Etiology				Total	Percentage of Total
	Syphilis	Syphilis and Hypertension	Rheumatic Fever	Syphilis or Arteriosclerosis		
Total number	93	5	2	45	145	100
Aortitis	59				59	40.6
Aortic insufficiency	1				1	0.7
Aortitis and aortic insufficiency	14				14	9.6
Aneurysm	12				12	8.3
Aneurysm and aortic insufficiency	5				5	3.5
Aortitis, aortic insufficiency and coronary disease	2				2	1.4
Aortitis and enlarged heart		5			5	3.5
Aortitis and rheumatic heart disease			2		2	1.4
Aortitis or arteriosclerosis of aorta				39	39	26.9
Aortitis or arteriosclerosis and fibrosis of myocardium				6	6	4.1

patients showed evidence of aortic insufficiency, and 11.8 per cent had aortic aneurysm. In only 2 cases was a diagnosis of narrowing of the coronary arteries due to syphilis made. This diagnosis was confirmed at autopsy in both instances.

Enlargement of the heart, often of marked degree, occurs, as is well known, when aortic incompetency has developed. The question whether the heart enlarges during the stage of aortitis and before the development of aortic insufficiency has not been answered clearly. Patients with uncomplicated syphilitic aortitis showed some degree of enlargement of the heart (19, or 32.2 per cent). When aortic insufficiency made its appearance the percentage rose (78.5). Patients with aneurysm without aortic insufficiency showed enlargement (41.7 per cent), especially when aortic insufficiency was also present (80 per cent, table 3). Enlargement of the heart was present, in short, in about one third of the patients with uncomplicated aortitis and in almost four fifths when aortic insufficiency had developed.

*Incidence of Cardiovascular Syphilis Relative to the Date of Infection*—Since we were particularly interested in discovering methods of recognizing cardiovascular syphilis early we classified our cases into five groups<sup>13</sup> according to the duration of the syphilitic infection, depending on whether evidence of cardiovascular disease appeared within three, from four to nine, ten to nineteen, twenty to twenty-nine or thirty or more years after the appearance of a chancre. The following data were obtained:

GROUP 1 In the first group, 8 cases (14 per cent) satisfied our criteria for the diagnosis of cardiovascular syphilis, all the patients showed aortitis and nothing else. Three other patients presented signs

TABLE 3—*Enlargement of the Heart*

Etiology	Anatomic Diagnosis	Total Number of Cases	Enlargement of Heart	
			Number	Percentage
Syphilis	Aortitis	59	19	32.2
	Aortic insufficiency	1	0	0
	Aortitis and aortic insufficiency	14	11	78.5
	Aortitis, aortic insufficiency and coronary disease	2	1	50.0
	Aneurysm	12	5	41.7
	Aneurysm and aortic insufficiency	5	4	80.0
	Total	93	40	43.0
Syphilis and hypertension	Aortitis and enlargement of heart	5	5	100.0
Syphilis and rheumatic fever	Aortitis and rheumatic valvular disease	2	1	50.0
Syphilis or arteriosclerosis	Aortitis or arteriosclerosis	45*	23	51.0
Total		145	69	47.6

\* Fibrosis of the myocardium was present in six cases.

of abnormality of the aorta in roentgenograms, and 5 others showed electrocardiographic abnormalities. The significance of these is discussed later. Forty-one (72 per cent) were entirely free from any signs of cardiovascular change. It should be stressed that only one of the entire group complained of symptoms referable to the heart (fig. 5).

GROUP 2 Of patients not seen in the clinic for cardiac disease until from four to nine years after primary infection, 6 (28.6 per cent) revealed the presence of aortitis, 2 of these presented also aortic insufficiency and 1 an aneurysm. Eleven were entirely free from any abnormality referable to the heart (52 per cent, as compared with 72 per cent in group 1). In case 2 the history of the symptoms was unreliable (fig. 6).

13 We included in these groups only those patients concerning whom the life history of the disease, from the occurrence of the chancre to the findings at the last examination, was known.

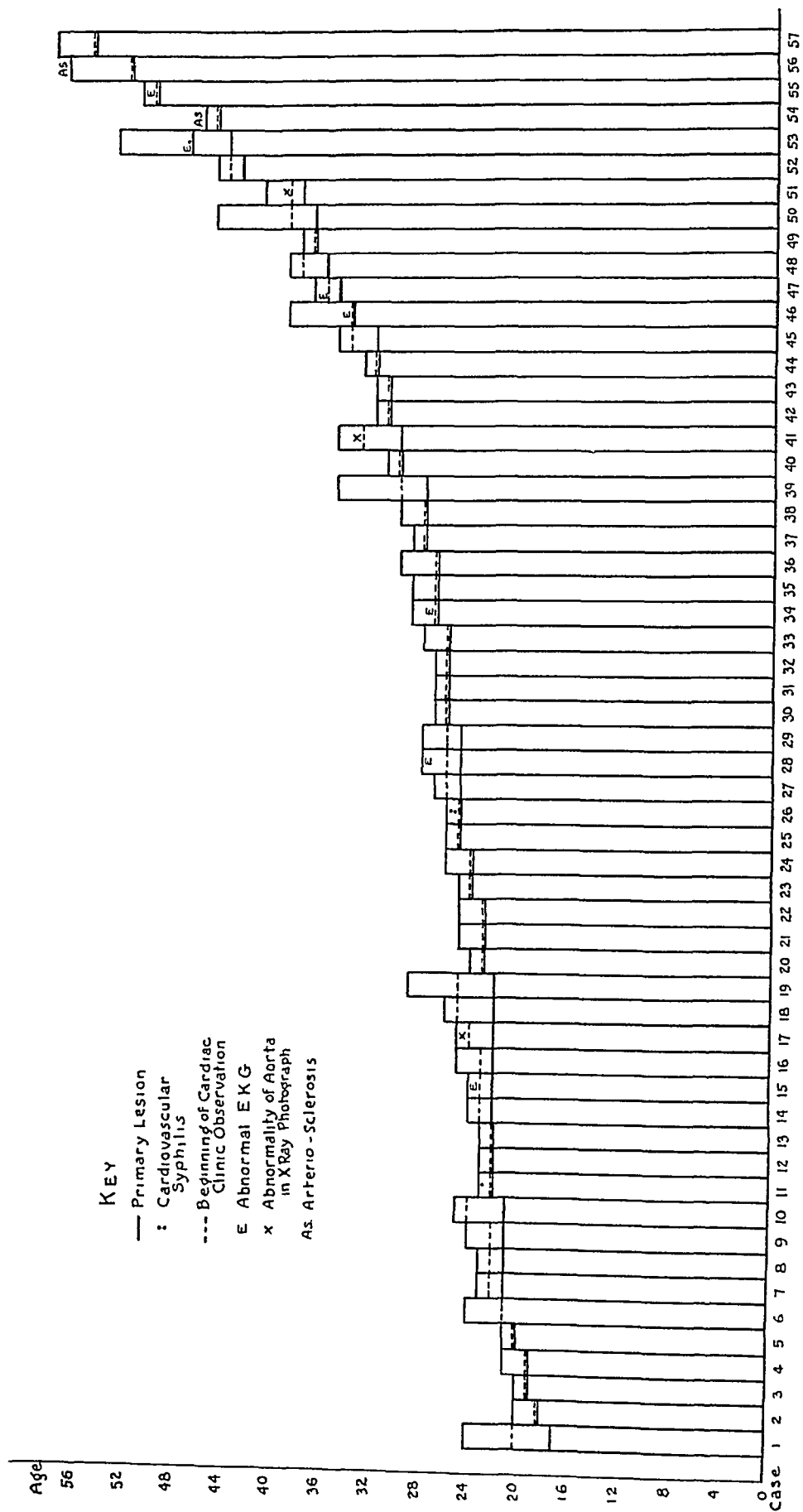


Fig 5 (group 1) —Data for patients at the beginning of observation in the clinic for cardiac diseases less than five years after the occurrence of the primary lesion In this and the following figures, E K G means electrocardiogram



Lamb and Turner<sup>11</sup> found few patients who presented symptoms or signs in the latent period (10 of 148). These died of some cause other than syphilis, though postmortem examination revealed the presence of syphilitic aortitis. Clinical evidence of cardiovascular syphilis developed, however, within less than ten years (in 12.3 per cent of the remaining 138 patients). The findings for this group differ slightly, the number affected within the first nine years being higher (18 per cent of 78 cases).

GROUP 3 Thirty-seven patients were referred to the clinic for cardiac disease from ten to nineteen years after infection. The incidence of cardiovascular syphilis among these is higher (in 21, or 56.8 per

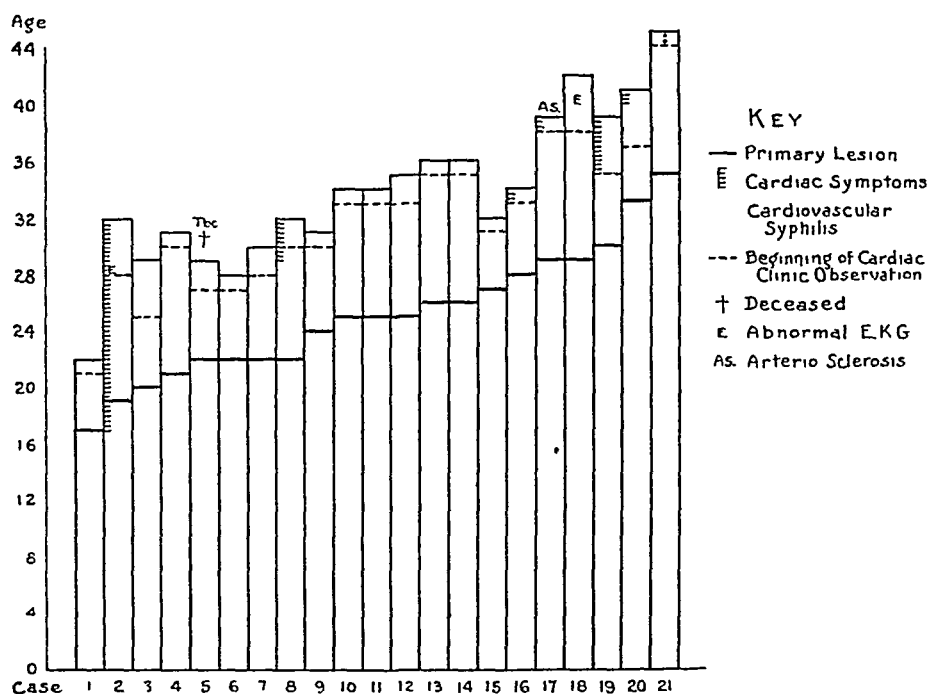


Fig 6 (group 2) —Data for patients at the beginning of observation in the clinic for cardiac diseases from four to nine years after the occurrence of the primary lesion

cent). Heart failure developed in 2 patients, 1 of these had two periods of decompensation due to aneurysm or aortic insufficiency and enlarged heart. In certain cases (10) some degree of arteriosclerosis was also present. Usually there were complaints of symptoms referable to the heart (in 9 of the patients with arteriosclerosis and 10 others). The number of those having symptoms rose from 28.6 to 51.3 per cent. Only 9 patients were entirely free from signs of cardiac disease (fig 7). Arteriosclerosis had, of course, begun to make its appearance in this group and may account for some of the symptoms.

GROUP 4 Syphilitic heart disease was present after a lapse of from twenty to twenty-nine years in three quarters of the cases (77.8 per

cent) Either aneurysm or aortic regurgitation appeared in 40 per cent, among them were 4 cases of heart failure (fig 8) Arteriosclerosis was now more commonly observed (in 44 per cent), and symptoms frequently made their appearance (in 78 per cent)

GROUP 5 Thirty or more years after infection syphilitic heart disease was present in all but 2 patients (15, or 88.2 per cent) Seven showed either aneurysm or aortic incompetence, and 4, heart failure

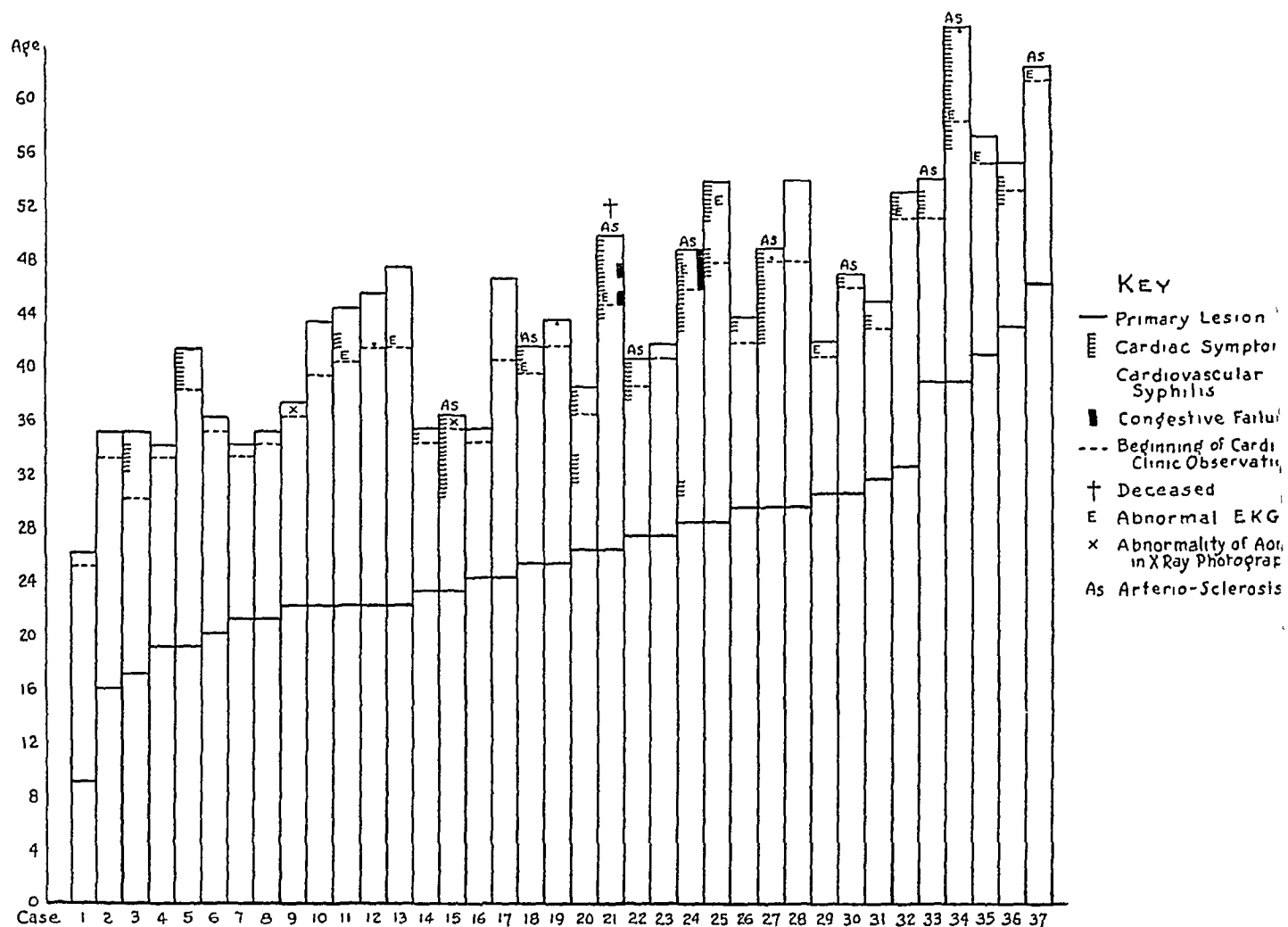


Fig 7 (group 3) —Data for patients at the beginning of observation in the clinic for cardiac diseases from ten to nineteen years after the occurrence of the primary lesion

complicated by aneurysm or aortic insufficiency or both Arteriosclerosis was frequent (in 12 patients), but in no instance was it the primary cause of heart failure Most of the patients in this group (76.5 per cent) complained of symptoms referable to the heart

Comment Certain patients in the five groups complained of cardiac symptoms before they came under observation This group was studied in greater detail It was found that in group 1, no patients, and in

group 2, only 1, complained of symptoms before the diagnosis of aortitis was made. These two groups together included all the patients in whom syphilitic infection was of short duration (less than ten years). Only 1 patient of the 14 complained of symptoms that might have led to the detection of aortic syphilis. As the duration of the infection lengthened and also as the patients grew older, symptoms began to make

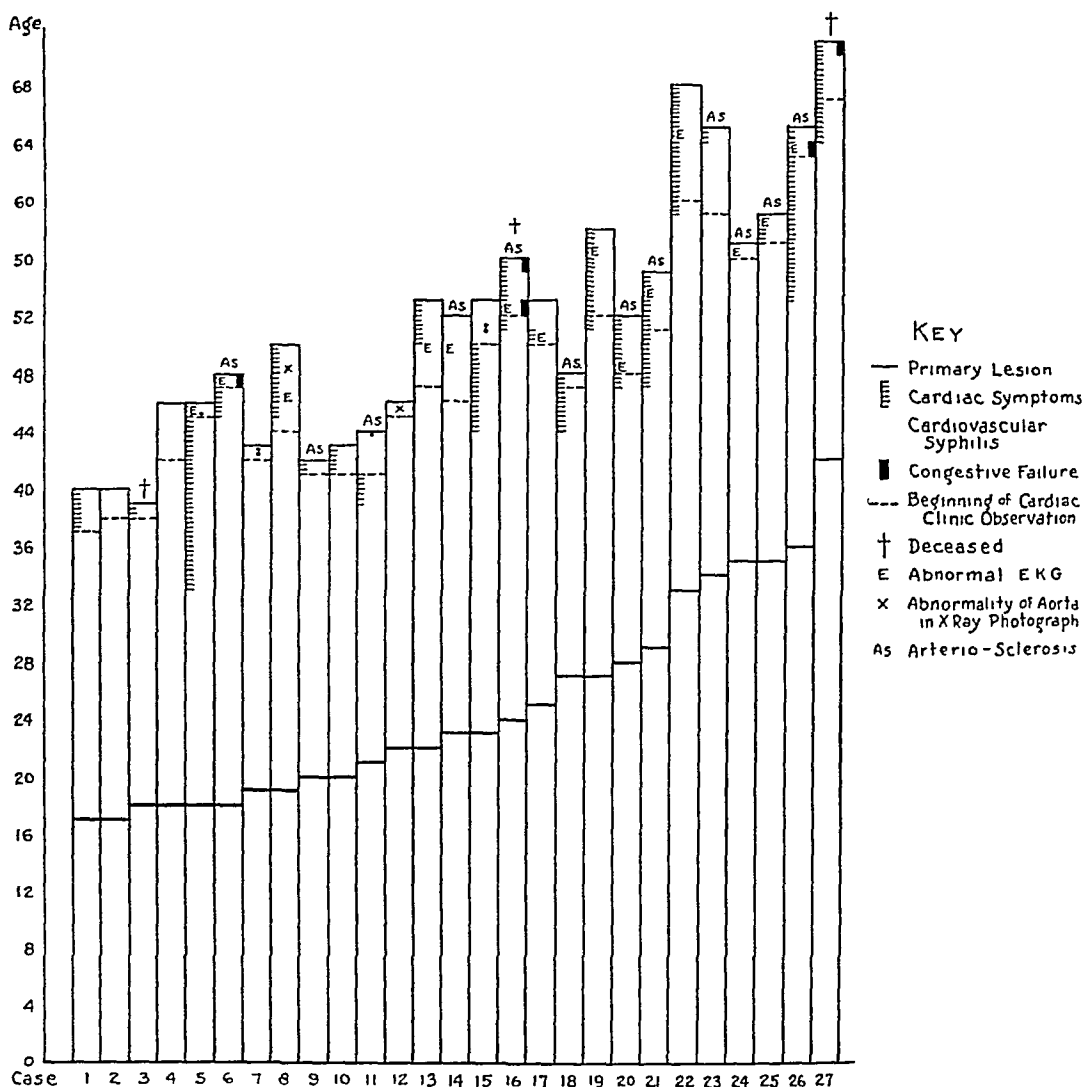


Fig 8 (group 4) —Data for patients at the beginning of observation in the clinic for cardiac diseases from twenty to twenty-nine years after the occurrence of the primary lesion

their appearance more often. In the early cases (those of less than ten years' duration) symptoms were not helpful in making a diagnosis.

The study of patients grouped according to the duration of the infection brought out strikingly the steady increase in the development of symptoms and lesions due to cardiovascular syphilis (table 4).

Symptoms tended not to be detected until after the discovery of aortic involvement in the younger groups. Finally, a steady increase was demonstrated in the appearance of cardiac symptoms in the older groups, even when no syphilitic involvement of the aorta had taken place.

*Changes in the Electrocardiograms*—An analysis was made of the electrocardiograms for those patients in whom the duration of syphilitic

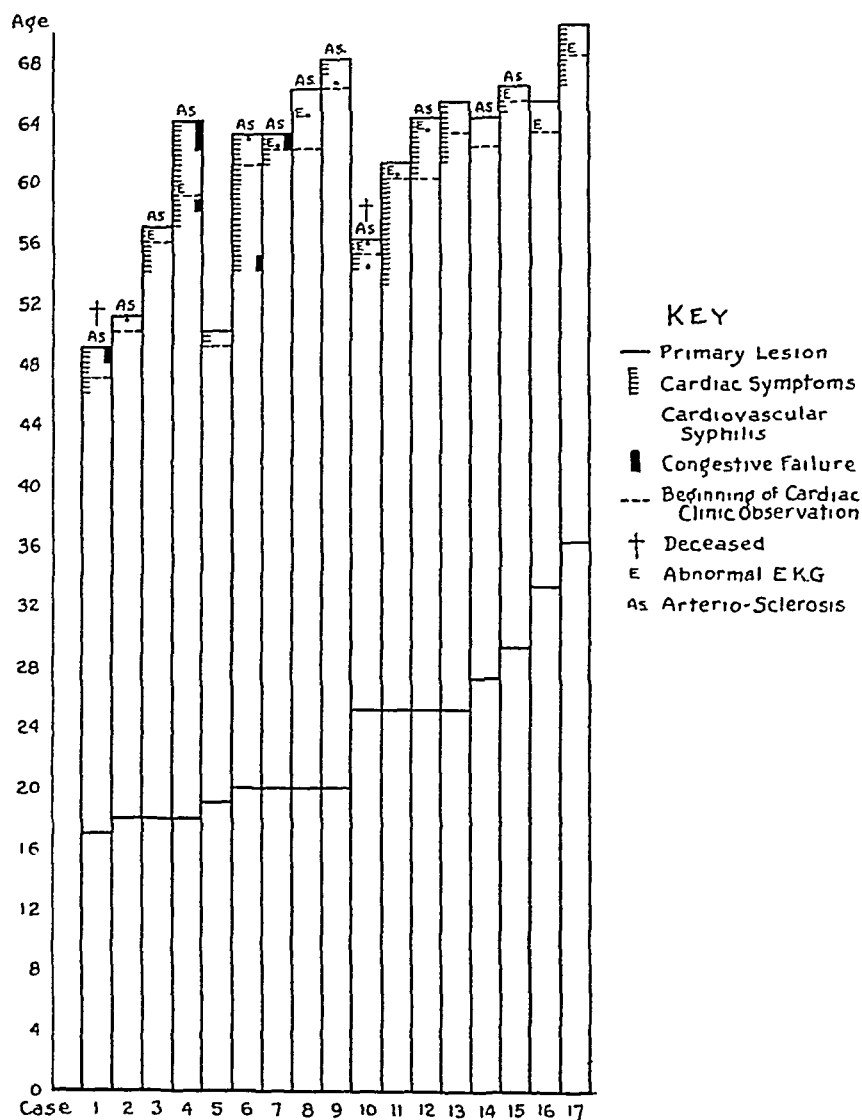


Fig 9 (group 5)—Data for patients at the beginning of observation in the clinic for cardiac diseases thirty or more years after the occurrence of the primary lesion

infection was known. All deviations from the normal were recorded and tabulated, but only those changes were studied which might be of clinical significance. These included auricular fibrillation, prolonged auriculoventricular conduction, partial heart block, low voltage and prolonged duration of the QRS complex, slurred and splintered QRS complex in all leads, depression or elevation of the ST segment and

significant negativity of the T wave. We found significant changes rarely in the early cases (in 10.4 per cent) when syphilis was the only etiologic factor. When arteriosclerosis and hypertension were also present the incidence of significant changes doubled (20 per cent).

After a longer duration the incidence of significant changes greatly increased (52 per cent). When other conditions played a rôle the incidence was lower (23.7 per cent), but since there were only 38 such cases the sample is too small to be of value for analysis. Within one year after the appearance of a chancre no changes were found in a former study<sup>14</sup>. Now, in a much larger series including the same patients significant electrocardiographic changes were still rare (in 10.4 per cent) after ten years.

*Postmortem Lesions*.—Of thirteen patients who died, 4 were examined post mortem. As was anticipated, lesions of syphilitic aortitis

TABLE 4—*Evidence of Cardiovascular Disease, Cardiac Symptoms and Heart Failure in Cases of Early Versus Late Syphilis*

Group	Years from Occurrence of Primary Lesion to Observation in Clinic	Num ber of Cases	Mean Age at Occurrence of Primary Lesion	Cardiovascular Syphilis		Cardiac Symptoms		Congestive Heart Failure		No Cardiac Abnormality	
				Num ber	Per centage	Num ber	Per centage	Num ber	Per centage	Num ber	Per centage
1	0-3	57	28	8	14.0					41	71.9
2	4-9	21	25	6	28.6	6	28.6			11	52.4
3	10-19	37	26	21	56.8	19	51.3	2	5.4	9	24.3
4	20-29	27	25	21	77.8	21	77.8	4	14.8		
5	30	17	23	15	88.2	13	76.5	4	23.5		

were present in all of them. In 3 there was aortic insufficiency, in 1 myocardial fibrosis and in 1 syphilitic disease of a coronary artery were also discovered. The width of the aortic shadows in roentgenograms of these 4 patients measured 6.6, 8, 9.5 and 10.3 cm., respectively. The first figure offers proof that syphilitic aortitis can occur when this measurement is between 6 and 7 cm. Besides aortitis, occlusion of a coronary artery due to syphilis, degeneration of the heart muscle and, in 2 instances, aneurysm of the arch of the aorta were present. There were no instances of syphilis of the myocardium, nor was a clinical diagnosis of syphilitic myocarditis made in the entire series of 346 patients. The changes in the myocardium were degenerative and due either to interference with the coronary circulation at the mouths of these vessels or to the effect of aortic insufficiency.

One case should be reported briefly because it furnishes further proof that syphilitic aortitis can develop to a marked degree within a short time after the appearance of a chancre.

14 Ingraham, R., and Maynard, E. P., Jr. The Electrocardiogram and Tele-roentgenogram in Early Syphilis, *Am Heart J* 6:82, 1930.

E S, a Negro, had a chancre in 1927, at the age of 35. The first symptoms referable to the heart were noted in October 1928. Disease of the heart was discovered in December, and he died of congestive heart failure in May 1929, two years after the onset of syphilitic infection. He suffered from anginal pain on exertion. A clinical diagnosis of syphilitic aortitis, aortic insufficiency and syphilitic disease of a coronary artery with myocardial failure was made. Syphilitic aortitis, occlusion of the right coronary artery 6 mm from its ostium due to syphilis and degeneration of the heart muscle were present<sup>15</sup>. The histologic diagnosis was syphilitic inflammation. There was an organized and canalized thrombus. The myocardium showed areas of recent myocardial softening and other areas of scar formation. The more recent areas were the larger. The vessels in the myocardial fat showed some thickening but no significant or characteristic internal changes. The areas of reaction in the myocardium contained numerous lymphocytes, newly formed fibroblasts and early scar tissue. In this case syphilitic aortitis had developed rapidly about strategic points—the openings of the coronary vessels. The nutritional damage to the myocardium was sufficient to cause death within two years.

*Congenital Syphilis*—Fourteen cases of congenital syphilis are included in this study. Seven patients showed no cardiovascular lesion whatever. Of the remaining 7, 2 exhibited evidence of rheumatic heart disease, 1 of congenital malformation of the heart, 1 of cardiac enlargement of unknown etiology and 3, in the fifth decade of life, of arterial hypertension, enlarged heart and widening of the aorta. A diagnosis of syphilitic aortitis was not made because of the presence of arterial hypertension.

The aortic shadows in the teleroentgenograms of these 14 patients measured between 6 and 6.9 cm. One, that of a man 54 years of age, gave aortic measurements of 6.2 cm, in another patient, 45 years of age, aortic enlargement occurred in association with arterial hypertension, and in a third in association with congenital malformation of the heart. There were 2 patients whose aortas measured more than 7 cm, but arterial hypertension was present in both. In each instance, when the aortic measurement was abnormal there was, therefore, some condition beside syphilis to which dilatation might be attributed.

In this group of patients with congenital syphilis there was none for whom we could safely make a clinical diagnosis of syphilis of the aorta.

*Duration of Disease*—Although this study does not concern itself with the prognosis, an attempt has been made to compare the course of events in these cases, with that studied by Grant,<sup>16</sup> who for ten years, beginning in 1919 to 1921, collected and analyzed the histories of 189 army pensioners, all of whom suffered from syphilitic aortic

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<sup>15</sup> Dr James Denton, pathologist at the Brooklyn Hospital, made the post-mortem examination.

<sup>16</sup> Grant, R. T. After Histories for 10 Years of a Thousand Men Suffering from Heart Disease, *Heart* 16:311 (June) 1933.

regurgitation Analysis of his histories shows that, on the average, his patients came under observation twenty-four years after initial infection—eleven years later than the average patient in the present study This difference is explained by the fact that Grant's series was limited to patients with aortic insufficiency or aneurysm, conditions which are not often diagnosed until late in the course of the disease When patients with these lesions alone are considered in the present study the interval between infection and first observation was, on the average, three years shorter than that reported by Grant Symptoms first appeared, on an average, twenty years after the occurrence of the chancre in both groups

It is not possible to make a comparison of the duration of life in the two series because the number of cases of aortic insufficiency in the present study is too small (15) to give it statistical significance and the number of patients who died is limited to 13 But Willius<sup>17</sup> made a study of 100 patients, having taken care to include only those for whom the date of infection and the date of death (the duration of the disease) were known The average duration was twenty-four years In a sample of 200 similar cases, DeGraff<sup>18</sup> found the average duration to be twenty-six years, and the interval from the onset of symptoms to death, 3 years Cabot<sup>19</sup> regarded these intervals as being even shorter—from fifteen to twenty years, and two years, respectively Grant concluded that "the prognosis, though poor, is not so gloomy as it is usually thought to be", he based this opinion partly on the fact that his patients have lived longer than the two or three years after observation usually assigned He ventured this conclusion because 38 per cent of his patients were still living at the end of his ten year period of observation

It should be pointed out, however, that the date of diagnosis is not a satisfactory point from which to relate the prognosis, because it varies with the skill of the observer and the time after infection when patients first present themselves Probably Grant's prognosis, based on the length of life after the first observation, is better than that of others, because by his method of selection through the army his patients came under observation sooner and their illness was diagnosed earlier The fact remains, however, that Grant did not take into consideration the date of infection of his patients Our analysis of his published case records reveals twenty-eight years as the average duration of the disease (from infection to death) for the deceased, while those who lived longer than his ten year period of observation have already lived an average of thirty-four years This living group, however, comprises

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17 Willius, F A A Study of the Course of Syphilitic Cardiovascular Disease, *Am Heart J* 6 113, 1930

18 Personal communication to the authors

19 Cabot, R C Facts on the Heart, Philadelphia, W B Saunders Company, 1926

only 19 patients<sup>20</sup> The mean duration from the onset of symptoms to death was seven and six-tenths years, while 66 surviving patients lived an average of thirteen years

It appears, therefore, that in cases in which the facts are known, the duration (from infection to death) of the disease was twenty-four years (Willius), twenty-six years (DeGraft) and twenty-eight years (Grant)—no great difference (fig 10) Among Grant's patients who were still living, the duration in 19 cases was, however, thirty-four years The interval from the onset of symptoms to death was two years (Cabot), three years (DeGraft), and seven and six-tenths years (Grant) Among Grant's patients who were still living the interval was thirteen years The last group was alive five years after the average duration of the disease in Grant's deceased patients This seems to point to the impropriety of separating the analysis of cases of living and dead patients

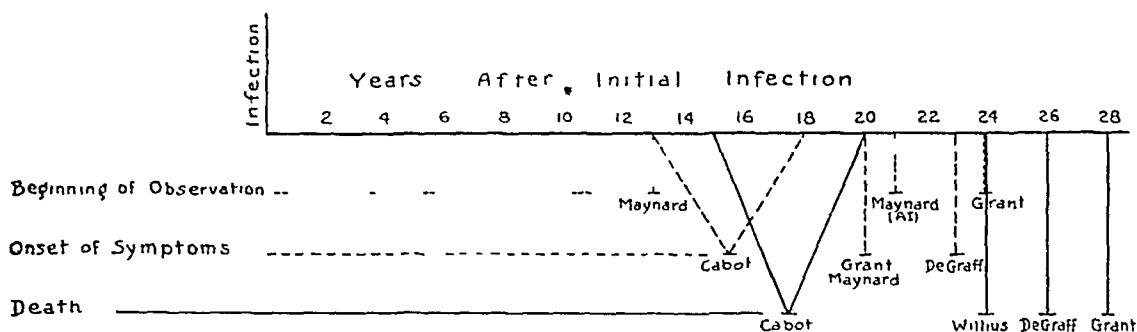


Fig 10—Factors pertaining to the duration of cardiovascular syphilis according to various observers The intervals expressed in this chart (from infection to the beginning of observation, the onset of symptoms and death) represent, in each case, mean averages

The fact that Grant's sample is made up of ex-service men, which necessarily excludes persons with cardiovascular syphilis who must have been rejected for military service because of advanced disease, as well as those who may have been recruited and yet not have survived the strain of the war, may account for this somewhat better prognosis than is usually reported Emphasis should be laid on the need for proper selection of cases if comparison is desired on the course of events in groups of cases studied in different clinics When groups of identical or similar composition are studied the likeness rather than the difference of the experience is striking It is possible that as our methods of diagnosis improve and as syphilitic patients come to be examined earlier and more carefully, the length of life from the time diagnosis is made to death may increase A true idea of the prognosis can, however,

<sup>20</sup> This group is limited to 19 patients because in the other instances the date of infection could not be ascertained



be obtained only by relating the duration of the disease to a definite period in its natural history—in this instance, the date of infection—rather than to arbitrary points of reference, such as the time at which physicians establish relations with given patients

#### GENERAL COMMENT

The present investigation was planned in order to study the natural history of syphilitic infection in relation to its effect on the cardiovascular system. Patients in the Brooklyn Hospital who were infected with syphilis were examined, with special attention directed to the heart and aorta. By this method it was hoped that syphilitic involvement of the aorta could be detected earlier than is customary. The high incidence of syphilitic aortitis that was found, namely, in 40.6 per cent of all the patients examined, seems to have justified this expectation. It emphasizes, furthermore, the necessity for periodic systematic examination, including the use of roentgenography and fluoroscopy.

Many authors have mentioned the sudden onset of symptoms of circulatory embarrassment as one of the essential points in the diagnosis of syphilitic aortitis. Carter and Baker<sup>21</sup> gave it as the first in their list of seven criteria for the diagnosis of cardiovascular syphilis. Moore, Dangle and Reisinger<sup>10</sup> found that symptoms were more often insidious than abrupt in onset and placed the nature of the onset of symptoms second only to the appearance in roentgenograms in diagnostic importance. Each of these studies was concerned with cases in which the disease was far advanced. In the present study it was found that symptoms referable to the heart were not helpful in making an early diagnosis of syphilitic aortitis. Those patients for whom this diagnosis was established within three years after the date of infection presented no cardiac symptoms whatever. Even when the group is included in which the diagnosis was made within ten years after the appearance of a chancre, symptoms referable to the heart were rarely encountered.

Physical signs, also, such as an accentuated hollow aortic second sound and an aortic systolic murmur, which are usually regarded as characteristic of this disease, were absent and could not be relied on in attempting to make an early diagnosis of syphilis of the aorta. The use of the roentgen method appears, however, to be extraordinarily valuable in deciding on the presence of aortitis in the absence of aortic insufficiency or aneurysm. The measurements usually accepted as descriptive of the normal aortic silhouette were found to be satisfactory, but reliance must, nevertheless, be placed on the skill of a competent

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21 Carter, E. P., and Baker, B. M., Jr. Certain Aspects of Syphilitic Cardiac Disease, *Bull. Johns Hopkins Hosp.* 48:315 (May) 1931.

roentgenologist in interpreting the form of the aortic shadows. Abnormal contours, especially of the ascending aorta, are important evidence in deciding on the existence of aortitis.

#### SUMMARY

Three hundred and forty-six patients with syphilis were studied. One hundred and forty-five (41.9 per cent) showed positive evidence of cardiovascular syphilis.

There were 14 adult patients with congenital syphilis. In none of these was evidence of syphilis of the heart or aorta found.

The date of occurrence of the primary lesion was known in about half of the patients (55 per cent). The average age at which infection occurred was 26 years. In a quarter of the patients studied the chancre appeared before the age of 21.

One fourth came for examination within one year, and one half within ten years, after the occurrence of the initial lesion.

Evidence of cardiovascular syphilis was found within ten years after the appearance of the chancre in one fourth of the cases, although the average interval from infection to the discovery of heart disease was twenty years. Symptoms were somewhat slower in making their appearance. One fourth of the patients complained of symptoms within fourteen years after the development of the primary lesion. The average interval before symptoms occurred was twenty years.

Evidence of cardiovascular syphilis was found within the first three years after the appearance of the chancre in 8 patients (14 per cent). One in the entire group complained of symptoms referable to the heart.

Of 21 persons who were not examined until four to nine years after primary infection, 6 (28.6 per cent) revealed the presence of cardiovascular syphilis. Two of these suffered from aortic insufficiency and one from aneurysm. Symptoms were present in 3 of the 6.

Among 37 persons who were not examined until ten to nineteen years after the primary lesion, 21 (56.8 per cent) exhibited evidence of cardiovascular syphilis. Symptoms appeared in 51.3 per cent of these. Heart failure occurred in 2 patients, in both of whom aneurysm or aortic insufficiency was present.

In a group first observed from twenty to twenty-nine years after infection, 77.8 per cent exhibited signs of syphilitic heart disease, 40 per cent presented either aortic insufficiency or aneurysm. Symptoms were present in 78 per cent.

Of 17 persons who were first examined thirty or more years after infection, 15 revealed the presence of cardiovascular syphilis, and 7 either those of aortic insufficiency or of aneurysm, three quarters of them complained of cardiac symptoms.

Heart failure occurred only in those patients in whom aortic insufficiency, aneurysm or involvement of a coronary artery developed

There were significant changes in the electrocardiograms within ten years after the appearance of the chancre in only 10.4 per cent. No changes were found that could be considered characteristic of the condition.

A case is reported of a patient whose condition was diagnosed as syphilitic disease of a coronary artery, who died within two years after the occurrence of the chancre. Postmortem examination confirmed the diagnosis.

#### CONCLUSIONS

1 Syphilis of the aorta can be recognized much earlier than in the past. In order to discover its presence it is necessary that every syphilitic patient be examined regularly by methods used in making a diagnosis of cardiovascular disease. These examinations should be repeated once in six months or once a year.

2 Roentgenograms and fluoroscopic examination provide the most reliable means of deciding whether abnormality of the aorta is present in early syphilis.

3 Heart failure occurs only in those patients in whom syphilitic involvement has passed beyond the stage of simple aortitis. In the patients studied myocardial failure appeared only after the development of aortic insufficiency, aneurysm or narrowing of the coronary arteries. Multiple gummas may be regarded as a cause of heart failure, but this condition was not encountered in this study. It is well known that these four manifestations are late lesions. Symptoms of heart failure usually prompt patients to seek relief in clinics for cardiac disease. Since these tend to occur late in cardiovascular syphilis and since no special routine effort has been made in the past to examine syphilitic patients for evidence of cardiovascular disease, the discovery of aortitis has been delayed. It is probably not true that syphilitic aortitis is a late lesion occurring, on the average, twenty years after the occurrence of the chancre. It is our opinion that involvement of the aorta begins soon after the chancre has appeared and that, in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination.

# CONFUSING CLINICAL MANIFESTATIONS OF MALIGNANT RENAL NEOPLASMS

C D CREEVY, M D

MINNEAPOLIS

Malignant renal tumors should be classed with syphilis and tuberculosis as among the great mimics encountered in clinical medicine. By direct pressure, by necrosis or hemorrhage, by extension or by metastasis they can reproduce the clinical appearances of an amazing variety of disorders. This fact is often mentioned but rarely emphasized in discussions of renal neoplasms. My attention was first attracted to this fact by 2 cases in which fever was a prominent feature.<sup>1</sup> Study of the cases of renal tumor at the University Hospitals and in the department of pathology of the University of Minnesota showed that in many cases the tumor had mimicked some other disease, particularly at the time of onset of symptoms, hence further investigation seemed advisable. With this end in view a group of 92 cases was studied.

## NOMENCLATURE

It is difficult to discuss neoplasms of the kidney without becoming involved with their nomenclature. For the sake of clarity this paper deals only with the malignant tumors of the renal cortex which are variously known as Grawitz tumors, hypernephroma (Birch-Hirschfeld<sup>2</sup>), nephroma (Bell<sup>3</sup>) or carcinoma (Wilson<sup>4</sup>). It is my opinion that these terms are synonymous and that arguments as to the propriety of one name as opposed to that of the others are fruitless.

## USUAL SYMPTOMS

It is probably desirable at this point to review briefly the usual clinical picture of neoplasm of the kidney. The classic triad of symptoms—pain, tumor and hematuria—is firmly fixed in the mind of every

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From the Division of Urology of the Department of Surgery, University of Minnesota Medical School

1 Creevy, C D. Pyrexia in Malignant Nephroma (Hypernephroma), *J A M A* **92** 1256 (April 13) 1929

2 Birch-Hirschfeld, F V. Beitrage zur pathologischen Anatomie der Nierengeschwulste, *Beitr z path Anat u z allg Path* **24** 343, 1898

3 Bell, E T. *A Textbook of Pathology*, Philadelphia, Lea & Febiger, 1930, p 262

4 Wilson, L B, and Willis, B C. A Comparative Study of the Histology of the So-Called Hypernephromata and the Embryology of the Nephridial and the Adrenal Tissues, *J M Research* **24** 73, 1911

medical student, probably because of the attractive adjective "classic," in spite of the fact that nearly every writer on the subject, particularly Braasch,<sup>5</sup> has been at some pains to point out that the three are present *together* only late in the course of the disease, long after the diagnosis should have been made

Hematuria is usually the most striking of the typical symptoms, and it is the most frequent (43 per cent of 367 cases of Judd and Hand<sup>6</sup>) The same authors obtained a history of pain in 37 per cent and of tumor as the initial symptom in but 14 per cent of their group The presence of any one of these symptoms in a person at the stage of life regarded as the cancer age demands a thorough urologic study In the last analysis the pyelogram is the only basis on which the diagnosis can be made with reasonable certainty, it should be obtained at a stage at which the symptoms are suggestive or but faintly suspicious Only then is it possible to take advantage of the notoriously slow growth and late metastases which so many renal tumors exhibit Even when these precautions are observed a considerable number of cases of renal tumor will inevitably be missed until after metastases have appeared because in many instances the latter occur before the primary tumor is large enough to cause any symptoms whatever

#### CONDITIONS RESPONSIBLE FOR CONFUSION

Certain characteristics of the malignant renal neoplasm are responsible for the confusing picture which it sometimes produces First among these is the tendency of such a neoplasm to grow very slowly Kjaft<sup>7</sup> had a patient whose history could be traced back for forty years, the tumor showed areas of cystic degeneration Israel<sup>8</sup> said that a history of twenty years' duration could often be elicited One of Ljunggren's<sup>9</sup> patients had had a palpable tumor for thirty years, and in Arkin's<sup>10</sup> case the growth was known to have existed for sixteen years, at operation it was calcified and partly ossified, nevertheless there was a prompt local recurrence Further evidence of the slow growth of malignant renal neoplasms is found in the number of patients

5 Braasch, W F Clinical Data on Malignant Renal Tumors, J A M A 60 274 (Jan 25) 1913

6 Judd, E S, and Hand, J R Hypernephroma, J Urol 22 10, 1929

7 Kraft, S Selbstheilung des Hypernephroms, Ztschr f urol Chir 5 16, 1920

8 Israel, J Ueber einige neue Erfahrungen auf dem Gebiete der Nierenchirurgie, Deutsche med Wchnschr 22 345, 1896

9 Ljunggren, E Studien uber Klinik und Prognose der Grawitzschen Nierentumoren, Acta chir Scandinav (supp 16) 66 1, 1930

10 Arkin, A Calcified Hypernephroma of the Kidney, Surg, Gynec & Obst 43 155, 1926

in whom metastases have developed years after the original tumor had been removed. A notable example is the case of Albrecht<sup>11</sup> in which a metastasis developed in the scapula four years after nephrectomy. It was removed, and the patient was still living nine years after the second, and thirteen years after the first, operation. As no local symptoms are produced until the renal pelvis, its capsule or adjacent organs are invaded, it is natural that such a tumor should remain symptomless for a long time.

This tendency toward slow, progressive invasion is of importance in view of the situation of the kidneys, since because of it a malignant renal tumor may simulate a primary lesion of the bowel, stomach, biliary tract or spleen.

A third characteristic which is often confusing is the extensive manner in which the tumor may metastasize. As Lehmann<sup>12</sup> has pointed out, the spread may take place either in an antegrade or in a retrograde fashion both by way of the venous system and via the lymphatics. Metastases from these neoplasms have been found in nearly every organ of the body. The percentage of cases in which metastasis is the first sign of illness is difficult to determine, but Deuticke<sup>13</sup> found it to be 9 and Israel 50 per cent.

#### PYELOGRAPHIC APPEARANCE OF RENAL NEOPLASM

The deformity as revealed in the pyelogram is usually characteristic, although it may at times be difficult to recognize. According to Braasch, five characteristic changes are noted, namely (1) elongation of one or more calices or of the pelvis, (2) encroachment on the pelvic lumen, causing flattening of the general pelvic outline, narrowing of the individual calices, obliteration of the true pelvis, obliteration of one or more calices or complete occlusion at or near the ureteropelvic juncture, (3) secondary pyelectasis, (4) abnormal position of the renal pelvis, and (5) deformity at the ureteropelvic juncture and upper portion of the ureter.

These changes vary markedly in extent. Probably the earliest type of recognizable change is exemplified in figure 1, a roentgenogram of an adenoma of the kidney, 2.5 cm. in diameter, which had just begun to invade a minor calix. Figure 2 shows the typical "spider-leg" deformity. Figure 3 illustrates an unusual change—multiple filling defects due to nodular intrapelvic projections of the tumor.

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11 Albrecht, P. Beiträge zur Klinik und pathologischen Anatomie der malignen Hypernephrome, *Arch f klin Chir* **77** 1073, 1905.

12 Lehmann, W. Hypernephrommetastasen des Skelettsystems, *Arch f klin Chir* **170** 331, 1932.

13 Deuticke, P. Nierentumoren, *Deutsche Ztschr f Chir* **231** 767, 1931.

## CONDITIONS SIMULATED BY RENAL NEOPLASMS

Renal neoplasms and their metastases mimic such a large and unrelated variety of disorders that any orderly classification is difficult. For convenience, the following arrangement has been employed: (1) metastases to the osseous system, (2) metastases to the lungs and pleura, (3) metastases to the digestive tract, (4) metastases to the female genitalia, (5) metastases to the neck, (6) metastases to the skin, (7)

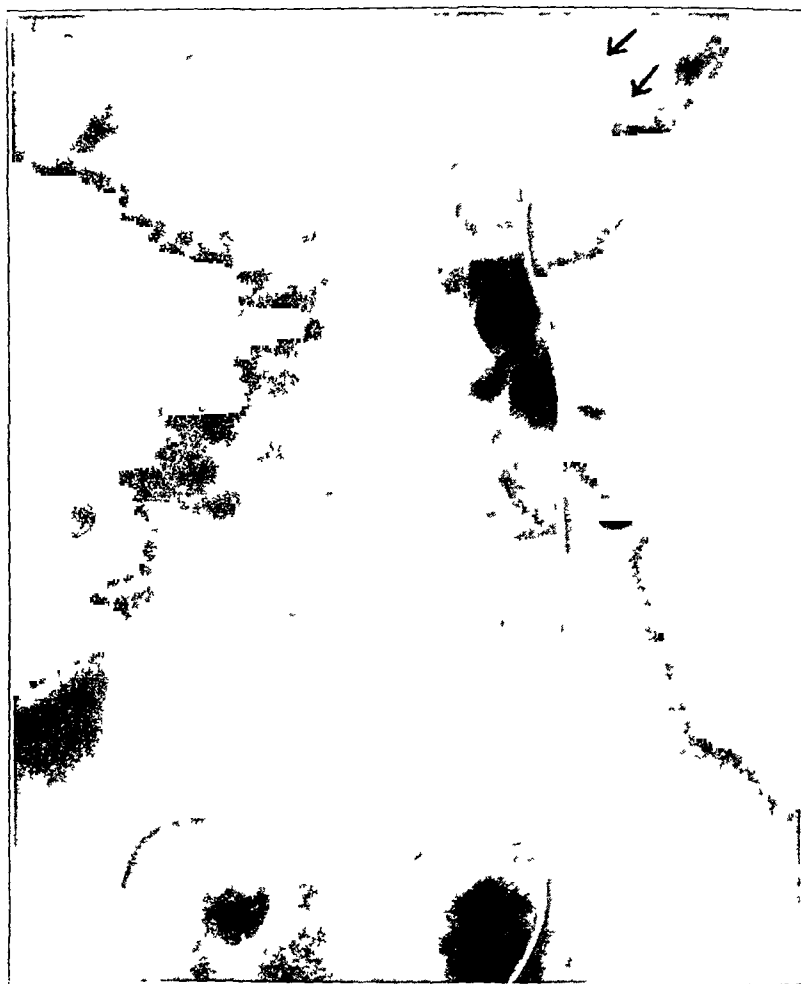


Fig 1—Early deformity from a renal neoplasm (adenoma)

metastases to the central nervous system, (8) metastases causing anemia, (9) metastases causing fever and (10) metastases simulating other disorders of the urinary tract. The osseous system is most often involved.

*Metastases to the Osseous System*—Lehmann collected reports of 56 cases of bony metastases from the literature. He found that in 9 of these there were multiple metastases and therefore the condition was rather obviously metastatic, in 13 either at autopsy or by prolonged

survival after removal the metastatic growth was proved to be solitary, while in 34 it was solitary as far as could be ascertained clinically. Twenty-four metastases were in the flat and 23 in the long bones, they occurred in the skull, sternum, clavicle, vertebrae, scapula, humerus, ulna, femur, tibia and tarsus. It is difficult to ascertain from the protocols given by Lehmann in what percentage of cases the solitary metastatic tumor was mistaken for a primary lesion, but the number of instances in which the diagnosis was suspected only after removal

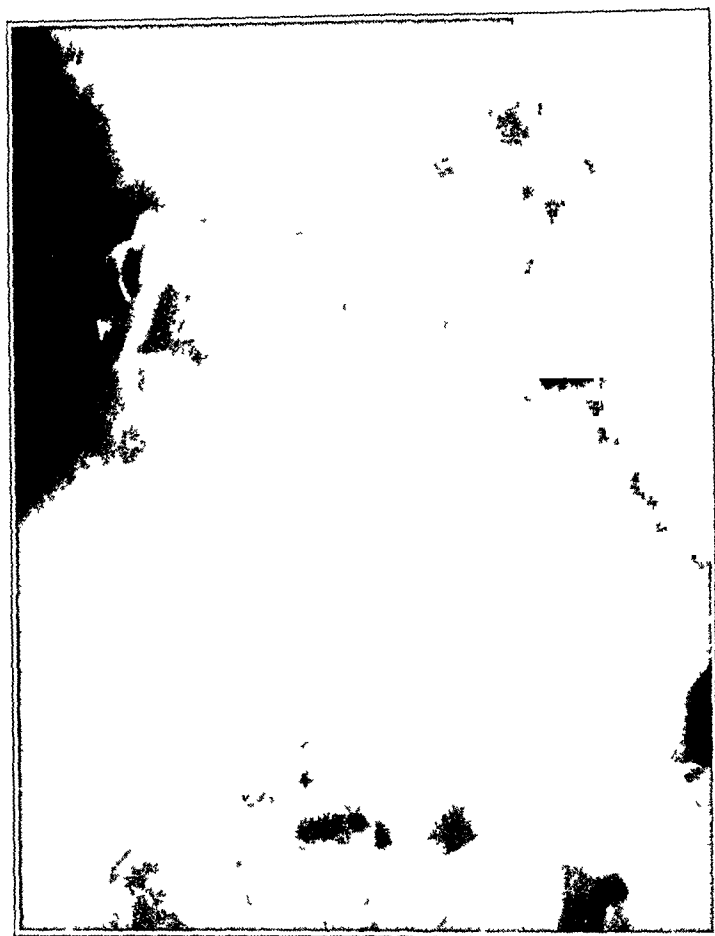


Fig. 2—Typical deformity of the renal pelvis from a neoplasm

and histologic examination of the metastatic deposit is rather high. In Schinz'<sup>14</sup> series of 10 cases, 3 were diagnosed correctly because of previous nephrectomy for hypernephroma, 3, after biopsy, and 3, only at autopsy. In 1 the metastatic growth was mistaken for a metastatic seminoma. In this case when the disease failed to respond to radiation therapy the diagnosis was changed to hypernephroma, this was later verified at autopsy. In the literature Schinz found that in 7 cases metastasis of hypernephroma to bone had been mistaken for osteogenic

<sup>14</sup> Schinz, H. R., and Uehlinger, E. Das Hypernephrom und seine Knochenmetastasierung, *Acta radiol.* **14** 56, 1933.



sarcoma, in 3, for tuberculosis, and in 1 each, for aneurysm of the aorta, metastasis from seminoma and primary giant cell tumor

The most reliable guide to a correct diagnosis is the appearance of the metastasis as revealed by roentgen examination. This appearance, while often fairly typical, is rarely so characteristic as to permit a final conclusion without the aid of pyelograms. Schinz has described two typical and several atypical varieties. The chief features are destruction of bone without expansion, periosteal reaction or formation



Fig 3—Multiple filling defects due to a hypernephroma

of new bone. The most easily recognized form presents a central oval defect, often with a pathologic fracture, in the diaphysis of a long bone. There is a similar picture in the flat bones which is equally characteristic and which Schinz called the "soap-bubble form." Less typical are ragged, oval areas of destruction with slight sclerosis at the margins. Occasionally such areas show sequestrums. Schinz observed one exceptionally puzzling case in which the lateral aspect of the femur was eroded and showed formation of new bone in the soft parts and a slight periosteal reaction which suggested a parosteal sarcoma.

To sum up one suspects the diagnosis from the roentgen appearance but makes it definitely only from the urogram. The physical character of the metastatic tumor is usually confusing rather than helpful.

*Metastases to the Lungs and Pleura*—Lesions in the lung less often cause confusion because by the time they become evident the primary tumor has usually attracted attention. However, Waser<sup>15</sup> reported the case of a patient who had been treated for pulmonary disease for five years before the true nature of the condition was recognized, and Vinson and Martin<sup>16</sup> made the diagnosis of metastasis after microscopic examination of a fragment of an apparently primary pulmonary tumor secured with the bronchoscope. The renal lesion was wholly symptomless.

The clinical appearance of a pulmonary metastasis is not typical unless the primary tumor has been discovered. There may be pain in the chest, cough and hemoptysis, but the lesion may be entirely symptomless. The physical findings are equivocal or absent as the metastasis may be so small or so placed as to escape detection. Thus dependence on roentgen examination is absolutely necessary. In roentgenograms metastases from renal tumor appear as single or multiple rounded areas of increased density which vary widely in size (fig. 4). They are rather sharply margined and have smooth edges, but not to the degree seen in secondary deposits from teratoma of the testis. Similar lesions may be produced by osteogenic sarcoma and occasionally by carcinoma of the rectum or breast or by some other neoplasm. Thus again, roentgen examination of the metastatic lesion is suggestive only and must be verified by pyelographic studies.

*Metastases to the Digestive Tract*—Two instances of metastasis to the tongue have been reported, one by Coennen and one by McKenzie and Waugh<sup>17</sup>. In the first the tumor of the base of the tongue and that of the kidney were both removed, and the patient was well five years later. In the second the patient died of generalized metastases, and the diagnosis was verified at autopsy.

Gastro-intestinal symptoms, chiefly postprandial epigastric distress, nausea and vomiting, are not uncommon in cases of surgical lesions of the kidney. In the majority of instances they are probably reflex in character, but in certain cases of malignant growth they are due to

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15 Waser, G. Schwere eigenartige Anaemie von hamolytischem Charakter bei nicht blutenden Hypernephrom, *Folia haemat* **26** 45, 1920.

16 Vinson, P. P., and Martin, W. J. Pulmonary Metastasis from Hypernephroma Diagnosed by Bronchoscopy, *Arch Otolaryng* **15** 368 (March) 1932.

17 McKenzie, D. W., and Waugh, T. R. Cystadenoma pseudopapilliferum Malignum of the Kidney with Metastasis in the Tongue, *J. Urol* **20** 121, 1927.

direct invasion of the stomach or bowel Grohe<sup>18</sup> and Thierry<sup>19</sup> have reported instances of invasion of the pylorus by a tumor of the right kidney which produced an obstruction requiring gastro-enterostomy The true nature of the lesion was recognized at autopsy Thierry also described the case of a physician in whom an acute intestinal obstruction developed which at operation appeared to be due to a tumor of the splenic flexure of the colon Recovery followed cecostomy, but the patient died of pneumonia following the surgical closure of the aperture

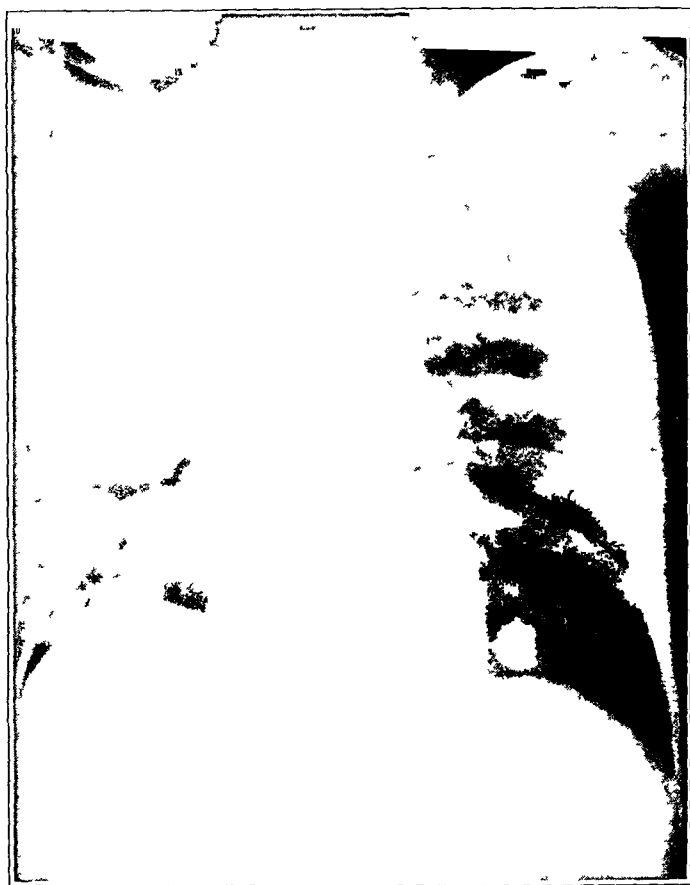


Fig 4—Pulmonary metastases

Autopsy disclosed a malignant neoplasm in the left kidney with a spontaneous perirenal hemorrhage which had compressed the bowel Direct invasion of the large bowel is not uncommon and may at times be amenable to resection and nephrectomy, as in a case described by Sugar<sup>20</sup>

18 Grohe, J B Unsere Nierentumoren in therapeutischer, klinischer, und pathologisch-anatomischer Beleuchtung, Deutsche Ztschr f Chir **60** 1, 1901

19 Thierry, H Beitrag zur Symptomatologie und Therapie des Hypernephroms, Munchen med Wchnschr **68** 638, 1921

20 Sugar, H Renal Neoplasm with Resection of Involved Colon, J Urol **24** 487, 1930

Scheele<sup>21</sup> and Albarran and Imbert<sup>22</sup> have observed jaundice from compression of the common bile duct. Garrow<sup>23</sup> had a patient who exhibited the typical symptoms of portal cirrhosis with weakness, gastrointestinal disturbances, pyrosis, ascites, edema and slight jaundice and in whom autopsy revealed a carcinoma of the right kidney which had occluded the renal vein and vena cava and invaded the regional glands.

Recognition of metastasis of the digestive tract is always difficult, particularly if the patient is first seen during an attack of intestinal obstruction, in such a case the diagnosis may be made at operation. In other situations correct diagnosis is largely a question of bearing in mind the possibility of renal tumor in atypical cases and of resorting to pyelography.

*Metastases to the Female Genitalia*—The female genitalia may be involved and present confusing symptoms. Gellhorn<sup>24</sup> found in the literature 14 instances of metastasis to the vaginal wall, most of which were identified only after histologic examination. Usually the lesion is a circumscribed, nonulcerated, submucous nodule which is easily enucleated and is attributed to retrograde metastasis from the renal vein along the ovarian vein. Grafenburg found such a lesion in the introitus adjoining the clitoris.

Garceau<sup>25</sup> and Funccius<sup>26</sup> have each reported cases of metastasis to the ovaries, and Garceau mentioned one instance of metastasis to the uterus. In Carey's case the neoplasm simulated ectopic pregnancy because of hemorrhage about a low-lying renal tumor, but the condition was recognized cystoscopically.

*Metastases to the Neck*—Occasionally a secondary deposit may appear in the neck, apparently propagated by way of the thoracic duct or supraclavicular glands (Deuticke, Israel, Claessen<sup>27</sup>). It is usually recognized by microscopic examination of excised tissue.

21 Scheele, K. Beitrage zur Klinik der Nierengeschwulste, Ztschr. f. urol. Chir. **10** 283, 1922.

22 Albarran, J., and Imbert, L. Les tumeurs du rein, Paris, Masson et Cie, 1906, p. 278.

23 Garrow, A. E., and Keenan, C. B. A Latent Hypernephroma with a Solitary Metastasis in the Spine, M. Rec. **81** 153, 1912.

24 Gellhorn, G. Vaginal Metastases of Hypernephroma, Am. J. M. Sc. **156** 94, 1918.

25 Garceau, E. Renal, Ureteral, Perirenal, and Adrenal Tumors and Actinomycosis and Echinococcus of the Kidney, New York, D. Appleton & Company, 1909, p. 43.

26 Funccius. Ueber von versprengten Nebennierenkeimen ausgehende Tumoren beider Nieren kompliziert durch Hufeisenmiere, Erlangen, Junge & Sohn, 1905.

27 Claessen, M. Die Verbreitungswege des Hypernephroms und die Beeinflussung der Geschwulstbildung durch Traumen, Breslau, Bresl. Genossensch.-Buchdr., 1919.

*Metastases to the Skin*—Metastatic nodules in the skin and subcutaneous tissues are not uncommon and present no difficulty because excision and examination are easily made, but a much less readily recognized lesion was described by Clairmont<sup>28</sup> and subsequently verified by Waser, Pleschner,<sup>29</sup> Deuticke and others. It consists of a peculiar bronzing of the skin, which involves the neck, the elbows, the areola of the nipples and the buccal and palatal mucosa and is due to the deposition of small, closely set dark flecks of pigment in the skin. There is a superficial resemblance to Addison's disease. Recognition depends on discovery of the lesion in the kidney.

*Metastases to the Central Nervous System*—Occasionally the first symptom is referable to the central nervous system. The metastasis may mimic a neuritis from compression or invasion of a nerve trunk by metastatic nodules—as in the case of Beig<sup>30</sup> in which a metastasis in the ischium involved the sciatic nerve—or a paraplegia secondary to compression of the spinal cord by vertebral metastasis (Deuticke, Garrow and Keenan). Intracranial involvement may mimic a primary tumor of the brain (Hoffman,<sup>31</sup> Huggins<sup>32</sup>).

*Metastases Causing Anemia*—Occasionally a case has been reported in which the symptoms resembled closely those of so-called primary anemia. In the case of Waser there was pigmentation of the skin, and the presence of pernicious anemia was suspected. After a period of observation a renal tumor was found. It is interesting that there had been no hematuria, the origin of the anemia was thus left in doubt. It is possible that bleeding into the tumor was responsible, since the hemoglobin content of the blood did not fall below 60 per cent.

*Metastases Causing Fever*—I have recently reviewed the subject of fever of noninfectious origin in cases of malignant tumors of the kidney. The condition was first recognized by Stetter<sup>33</sup> and was found by Israel in 18.2 per cent of all the cases he observed. He distinguished initial, intercurrent and terminal types, dividing each into hectic, recurrent and hematuric and suggested that when infection was absent the elevation of temperature was due to the formation in the tumor of a

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28 Clairmont, P. Beiträge zur Nierenchirurgie, Arch f klin Chir **79** 667, 1906.

29 Pleschner, H. G. Beiträge zur Klinik und pathologischen Anatomie der malignen Hypernephrome, Ztschr f urol Chir **1** 309, 1913.

30 Berg, A. A. Malignant Hypernephroma of the Kidney, Surg, Gynec & Obst **17** 463, 1913.

31 Hoffman. Hypernephrommetastasen, Zentralbl f Chir **34** 82, 1907.

32 Huggins, C. B. Hypernephroma Without Symptoms or Signs, S. Clin North America **9** 382, 1929.

33 Stetter. Demonstration eines exstirpirten Pyloruscarcinoms und einer exstirpirten carcinomatösen Niere, Verhandl d deutsch Gesellsch f Chir **16** 36, 1887.

pyrogenic substance While the source of the fever may be obvious it may, as in Nicholson's<sup>34</sup> case, be the only symptom and cause extreme difficulty in diagnosis

*Metastases Simulating Other Disorders of the Urinary Tract*—Occasionally, even though the tumor produces symptoms directly referable to the urinary tract, the diagnosis may be obscure because of the atypical nature of the symptoms, especially when no tumor is palpable Since, as Ljunggren has pointed out, a tumor of the kidney in order to be palpable must be at least as large as a man's fist—unless it is in the anterior surface of the lower pole or unless the patient is emaciated—such confusion is potentially frequent Clots of blood may cause retention of urine and produce symptoms similar to those of tumor of the bladder or of obstruction of the vesical neck (Pleschner) An inexperienced cystoscopist may mistake the clots for a neoplasm in the bladder

Squier<sup>35</sup> reported two instances in which shadows in the roentgenograms of patients with renal colic and hematuria were mistakenly regarded as being caused by stones when they actually represented areas of calcification in a tumor In a third instance the shadows were due to stones coexisting with a neoplasm Crane<sup>36</sup> had a patient with a small and previously symptomless tumor beneath the capsule which was recognized only because it caused a perirenal hematoma which led to operation

#### REVIEW OF CASES

*General Considerations*—Ninety-two cases of malignant neoplasms of the parenchyma of the kidney have been reviewed in an effort to ascertain how frequently the presenting symptoms were such as to cause confusion with symptoms of some other lesion Forty-six of these cases were found in the autopsy material of the Department of Pathology at the University of Minnesota and 46 in the clinical records of the University Hospitals In assembling the material 30 cases of tumors were rejected because they represented only incidental findings in patients who died of other, wholly unrelated, conditions These tumors were small, encapsulated and located at a distance from the calices and pelvis and played no part in causing the patient's symptoms or death No cases are included in which reasonable doubt existed as to the existence of a renal tumor or of its rôle in producing the symptoms of which the patient complained

34 Nicholson, D Fever with Renal Carcinoma, Arch Path 3 393, 1927

35 Squier, J B Neoplasms of the Kidney and Ureter, Boston M & S J 161 547, 1909

36 Crane, W J Renal Tumor, Unusual Complication Leading to Early Diagnosis, J Urol 22 535, 1929

The impression produced by a survey of the 92 cases is not a pleasant one. In the autopsy series since the patients died of renal tumor, the incidence of metastases was naturally high (43 of 46 cases, or 93.5 per cent). It was surprising to learn that there had been demonstrable secondary deposits in 35 (76 per cent) of the cases in the clinical series. This figure is especially striking when one considers that before 1925 roentgen examinations of the chest were not made as a routine, hence the true incidence of metastasis must be still higher.

TABLE 1—*Location of Secondary Lesions in Seventy-Eight Cases of Renal Neoplasm in a Group of Ninety-Two Cases*

Location	Number of Lesions		
	Autopsy Series	Clinical Series	Total Series
Bones	23	23	51
Lungs	28	12	40
Liver	16	3	19
Regional glands	13	3	16
Opposite kidney	11	1	12
Renal vein	7	4	11
Vena cava	7		7
Adrenal gland	7		7
Brain	5	1	6
Pancreas	4	1	5
Pleura	3	2	5
Diaphragm	3	1	4
Peritoneum	2	2	4
Colon	3		3
Omentum	2	1	3
Pericardium	2	1	3
Small bowel	2	1	3
Gallbladder	2		2
Supraclavicular glands		2	2
Mediastinal glands	2		2
Mesenteric glands	2		2
Neck	1	1	2
Heart	2		2
Spleen	2		2
Stomach		1	1
Ovarian vein	1		1
Iliac vein	1		1
Femoral vein	1		1
Skin	1		1
Buttock	1		1
Perineum (male)	1		1
Urethra	1		1
Testis		1	1
Epididymis	1		1
Ureter	1		1
Bladder		1	1
Total	158	67	225

The interesting feature in both series of cases for the purposes of this paper is the fact that the symptom which caused the patient to consult a physician did not in any way suggest the existence of a renal neoplasm as a causative factor in 41.3 per cent of the whole group. The incidence of atypical cases was, for obvious reasons, somewhat higher in the autopsy series (50 per cent) than in the clinical series (32.6 per cent) since autopsy is more often performed in confusing or obscure than in clearcut cases.

It seems worth while to digress in order to enumerate the astonishing number of organs in which metastases or extensions were found (table 1). Thirty-six organs or systems were involved a total of 225 times. As is usual in most series, the bones (table 2) and the lungs were most frequently affected.

Certain discrepancies in the table require explanation. It will be noted that involvement of the pericardium occurred once in the clinical series. As a matter of fact, the condition was found at autopsy, in 12 of the cases in the clinical series necropsy was performed, but these cases have been classed with their original series. The greater incidence of metastasis to the other kidney and to the renal vein, vena cava and regional glands observed in the necropsy series is due to the greater accessibility of these structures for pathologic examination, the more frequent involvement of the humerus as revealed clinically is probably

TABLE 2—*Distribution of Fifty-One Metastatic Lesions of Bone*

Location	Number of Lesions		
	Autopsy Series	Clinical Series	Total Series
Spine	7	6	13
Pelvis	4	4	8
Ribs	4	3	7
Humerus		6	6
Femur	3	3	6
Skull	2	3	5
Mandible		1	1
Clavicle		1	1
Sternum	1		1
Scapula		1	1
Tibia	1		1
Fibula	1		1
Total	23	23	51

due to the pathologist's reluctance to mutilate the body unnecessarily. Unquestionably necropsy or roentgen examination of all the bones as a routine procedure would increase enormously the number of cases in which bony metastases are recognized.

#### ATYPICAL CASES

To return to the original problem of the cases presenting confusing or atypical symptoms at the onset, tables 3 and 4 show what a variety of pathologic conditions have been simulated. Here again bony metastases head the list (16 of 38 cases), and pulmonary metastases are a fairly close second. In the autopsy series, pain in the spine (most often in the lumbar or sacral region) frequently constituted the patient's first complaint, not uncommonly this symptom occurred after a slight trauma which probably called attention to a preexisting but hitherto painless lesion. In the clinical series a secondary deposit in the humerus was most often the first sign of illness. In all, four patients sustained



pathologic fractures of that bone after slight injuries (fig 5), in only one had a tumor in the bone been noted first. None had any of the classic symptoms of renal tumor, and the presence of such a tumor was demonstrated by pyelography.

The literature states that metastases to bone often pulsate, this was not true in any of the cases observed in the clinical series, the tumor was palpable in only 3 and it was solid in all. Although instances of solitary bony metastasis are often reported, in all the cases in this

TABLE 3—*Conditions Simulated by the Metastasis or Extension of Renal Neoplasms*

Nature	Number of Autopsy Series	Number of Clinical Series	Number of Total Series
Tumor of the bones	10	6	16
Spine	5	1	
Humerus		4	
Femur	2		
Pelvis	1		
Tibia	1		
Skull	1		
Clavicle		1	
Pulmonary disease	5	4	9
Tumor of the brain	2		2
Encephalitis		1	1
Myelitis	1		1
Neuritis of the brachial plexus	1		1
Tumor of the neck	1	1	2
Portal cirrhosis	1	2	3
Carcinoma of the stomach		1	1
Intestinal obstruction	1		1
Periurethral abscess	1		1
Total	23	15	38

TABLE 4—*Conditions Simulated by the Tumor Itself*

Nature	Incidence
Tumor of the bladder	2
Nephrolithiasis	1
Ovarian cyst	1
Total	4

\* All the figures given in this table are from the clinical series.

group the metastases were multiple. As was pointed out earlier, the diagnosis usually depended on the suspicion as to the existence of the osseous lesion as aroused by the roentgenograms and was verified by pyelography. In one case in the autopsy series the diagnosis was made during life by examination of material curetted from what appeared to be a cyst in a bone, and in another it was made only at autopsy, the patient having died shortly after he sustained a pathologic fracture of the femoral neck.

One may say that the presence of metastatic tumor of the kidney should be suspected in any atypical, destructive lesion of bone in a middle-aged or elderly patient especially if the lesions are multiple,

the metastasis as well as the primary tumor may be impalpable so that in many instances one is completely dependent on the roentgen examination. In suitable cases biopsy may be employed, particularly if the lesion is in the subcutaneous bones. Nevertheless, in a few cases the condition will not be recognized except at autopsy.

In 9 of the 38 confusing cases the patient first sought advice because of symptoms referable to the lungs, usually in the form of cough, pain in the chest and hemoptysis. Two cases presented particular difficulty. In 1 the diagnosis was not made until typical lobal pneumonia failed to resolve, roentgen studies then showed typical metastases, and subsequent pyelography established the diagnosis. In another, the condition



Fig. 5—Metastases to the humerus with pathologic fracture

developed in a patient discharged a few years before from a sanatorium where tubercle bacilli had been found in the sputum. In the remainder the complaints already noted were present, and the condition was recognized by roentgen examination.

In 2 cases in which autopsy was performed there were symptoms of an unlocalizable lesion of the brain and, in the complete absence of urinary symptoms or palpable tumors, the condition was not recognized during life. There is nothing characteristic about these cases. In 1 case in the clinical series there was a history suggestive of encephalitis in that the patient often fell asleep at the dinner table, he complained of stiffness of the neck and back and of generalized headaches. The absence of definite findings led the neurologist to suspect the presence of an abscess of the brain or a tumor possibly, because of the atypical

character of the findings a metastatic hypernephroma. Urologic consultation was asked, but because the patient was obviously moribund cystoscopic examination was not made, intravenous urograms were unsatisfactory. Autopsy showed extensive cerebral metastases.

In this case again the diagnosis depended on suspicion aroused by atypical cases and verified by pyelography. It may be noted at this point that intravenous urography has not been wholly satisfactory in establishing a diagnosis of renal tumor at the University Hospitals. Retrograde pyelograms have been required in nearly every case because the impairment of renal function by the tumor has prevented adequate visualization of the diseased kidney.

In another instance paraplegia with sphincteric incontinence developed in a middle-aged patient when he fell from a truck and struck his spine. Several months later roentgen studies revealed metastases in the lumbar portion of the spine. While there is a considerable amount of speculation in the literature as to the relationship between trauma and the development of metastases, especially in bone, it is futile to theorize here. It seems logical to suppose that there was a hemorrhage into a metastasis in the cord at the time of the injury, since roentgenograms made shortly thereafter showed nothing abnormal. This was a case of the type which usually continue to escape diagnosis until necropsy, since there were no symptoms to identify either the primary tumor or the metastases.

Another patient presented neuritic symptoms referable to the brachial plexus. Sufficient details are not available as to physical findings.

Among the obscure cases must be listed that of a man, aged 62, who had been admitted to the hospital with vague abdominal discomfort and intermittent edema of the ankles and who was dismissed after considerable study with a diagnosis of possible malignant tumor of undetermined location. He returned seven years later with a slowly growing mass beneath the lower end of the left sternocleidomastoid muscle. The tumor was as large as an apple and was hard, nodular and fixed. The right kidney was palpable, and the superficial abdominal veins on the right side were distended, they transported blood upward. The pyelogram of the right kidney showed a typical renal neoplasm. Biopsy of the mass in the neck showed "hypernephroma" (fig 6).

A similar case was found in the autopsy series. A man, aged 83, had complained of a cough, dyspnea and hemoptysis of six months' duration, these symptoms were complicated two months before hospitalization by evidence of a tumor in the lower anterior part of the neck on the left side. The patient died shortly after aspiration of the left pleural cavity, autopsy revealed a small hypernephroma on the left side. It had metastasized to the lungs, regional glands and left supraclavicular lymph nodes.

In 2 cases renal tumors mimicked hepatic cirrhosis and disease of the biliary tract. In 1 of these, a woman aged 30 had noted weakness, dyspnea, cough and edema of the ankles for four years, and two years before admission chills, fever, pain in the right upper abdominal quadrant and jaundice had developed. An abdominal exploration in another hospital had shown apparent cirrhosis of the liver and chronic cholecystitis. After cholecystostomy there was temporary improvement, but two years later mild jaundice, ascites and edema developed. The urine was normal. The patient died shortly after admission to the hospital, and the necropsy demonstrated that the supposed cirrhosis was due to

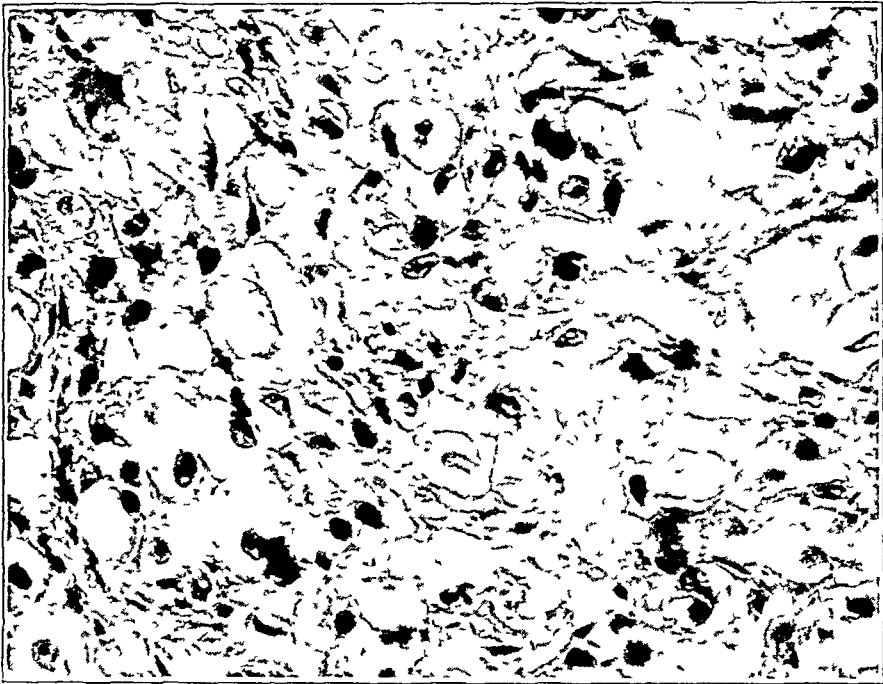


Fig 6—Microscopic appearance of a hypernephroma metastasizing to the neck

multiple nodular tumors secondary to a carcinoma of the right kidney which had extended into the renal vein and vena cava.

Two cases so similar to the last that they need not be described in detail were found in the autopsy series.

One patient, aged 55, in the clinical series presented a typical picture of carcinoma of the stomach, with a recent loss of weight of 25 pounds (11.3 Kg), anorexia, pain in the epigastric region after eating and vomiting. There was an ill defined mass in the left upper quadrant of the abdomen, and severe anemia was present, the urine contained a few white blood cells. However, ordinary roentgenograms of the abdomen showed erosion of the left margin of the upper two lumbar vertebrae (fig 7), roentgenograms of the gastro-intestinal tract showed only displacement of the stomach and colon, and a pyelogram of the left kidney showed conditions typical of renal neoplasm. The patient

failed rapidly and died. The digestive disturbances could probably be explained by invasion of the ileum which was found post mortem.

In another case in the autopsy series symptoms of a gastro-intestinal lesion were present in a patient who sought aid for a typical acute intestinal obstruction coming on with few premonitory symptoms. Exploration established the fact that the obstruction was due to infiltration of the splenic flexure of the colon by a growth in the left kidney. The



Fig 7—Erosion of the bodies of the vertebrae by a hypernephroma of the left kidney

patient died in spite of a colostomy for the obstruction, and autopsy verified the diagnosis.

Only once in the whole group was there confusion between a renal neoplasm and a lesion of the female genitalia. A woman, aged 66, had twice received radium for metrorrhagia before a smooth, rounded, freely movable mass was noted in the right lower quadrant of the abdomen, it was palpable also on pelvic examination. The urine was normal. A diagnosis of ovarian cyst with uterine bleeding was made, but a carcinoma in the lower pole of a movable, ptotic kidney was found at operation and removed through a median subumbilical incision.

In 4 cases a renal neoplasm was mistaken for another type of lesion of the urinary tract

The first of these was in a man, aged 53, who had had renal colic on the right side and hematuria and had passed stones at frequent intervals for two years. An ordinary roentgenogram of the urinary tract showed shadows in the region of the right kidney, on pyelography these shadows appeared to be included in the renal pelvis, which also contained many irregular shadows thought to be soft stones (fig 3). At operation, however, there was found a large hypernephroma which invaded the pelvis, producing the irregular shadows, two stones were also present. In this case the error was one of interpretation of the pyelogram, since the symptoms were undoubtedly due to nephrolithiasis.

In two other cases a diagnosis of tumor of the bladder had been based on cystoscopy by the family physician. In each there was a history only of painless hematuria, culminating in one case in urinary retention due to the formation of a clot. In neither was there any palpable mass, and in both cystoscopy demonstrated renal bleeding, and pyelography, renal neoplasms. These cases, of course represent confusion of blood clots with vesical neoplasms, an error easily avoided if a biopsy is made on tissue removed by means of the cystoscope, since an attempt to secure tissue makes the nature of the mass in the bladder clear.

In one case in which the primary tumor was known to exist a metastasis to the bladder was suspected at cystoscopy, but this was not verified by microscopic examination. The ureteral metastasis in the autopsy series was an incidental finding.

In the final case to be mentioned (from the autopsy series) a man, aged 37, suffered from backache in the region of the sacrum and from low grade, intermittent fever for several months before a swelling of the left side of the scrotum and urinary retention developed simultaneously. Catheterization was followed by the development of a tender, hard mass in the penoscrotal angle. It was thought to be a perimethral abscess, but incision showed the mass to be solid, on microscopic examination it suggested a necrotic adenocarcinoma. The patient died twenty-four hours after amputation of the penis, and necropsy disclosed a hypernephroma of the left kidney with metastasis to the lungs, liver, regional glands and left epididymis.

This is a case of the type which defies clinical recognition.

#### COMMENT

There is no doubt that a fairly high percentage of the cases of renal neoplasm will continue to escape recognition until late in their course not merely because patients are prone to delay medical consultation and

because the disease often produces syndromes difficult to identify, but chiefly by reason of the fact that the first symptom to attract the patient's attention is so often due, not to the tumor itself, but to a metastasis or local extension. This was the case in 32.6 per cent of the cases in the clinical series, in 50 per cent of those in the autopsy series and in 41 per cent of those in the whole group—a disconcertingly high proportion.

This is a situation which cannot at present be fully met in any practicable manner. To be sure, a painstaking eliciting of the history would perhaps have revealed facts which would have brought up the question of renal neoplasm, particularly if there was a hematuria which had been forgotten by the patient, or a brief attack of renal colic. A more careful physical examination in obscure cases may be helpful, but it is of uncertain value, since many normal kidneys are palpable and since many large tumors escape detection. The key to the whole problem lies in considering the possibility of a malignant renal tumor in every case of an obscure ailment, particularly in cases of tumors of the bone, of unusual lesions of the lungs, gastro-intestinal tract and nervous system and of obscure fever or anemia. In the investigation of such conditions intravenous urography is a valuable diagnostic aid because it spares the patient the discomfort of a cystoscopy. It is true that it may often impede a positive diagnosis because the affected kidney fails to excrete the dye, nevertheless such an event focuses attention on the kidney and may lead to a positive diagnosis with the aid of a retrograde pyelogram. On the other hand if two normally functioning and normally formed pelvises are demonstrated, the possibility of renal neoplasm is rather definitely excluded.

The question cannot be discussed without a mention of solitary metastasis, chiefly because there are on record several instances in which microscopic examination of a supposedly primary tumor after its excision led to the recognition and removal of a hypernephroma and to the survival of the patient for periods up to thirteen years. There was no case of solitary metastasis in this group, however, Lehmann found that in 13 of 56 cases of metastatic hypernephromas of bone recorded in the literature the metastasis was solitary as shown either at autopsy or by prolonged survival of the patient after operation, in 34 additional cases it was solitary as shown clinically. While it should be pointed out that most of this material comes from reports suggesting the advisability of surgical intervention and hence does not represent a true picture of actual conditions instances of solitary metastasis apparently do occur. If after painstaking search, a metastatic tumor of the bone proves to be solitary its removal together with that of the primary lesion may be considered.

It must be admitted that the questions involved here are, in a sense, largely academic, since once it has been determined that one of these obscure disturbances is due to a primary malignant tumor of the kidney there is usually little hope of cure except in instances in which another disease of the urinary tract has been simulated. However, the accurate identification of these cases will save many unnecessary operations and much futile treatment and will permit a more accurate prognosis.

#### SUMMARY AND CONCLUSIONS

The first symptom of a malignant neoplasm of the kidney is often due, not to the primary tumor itself, but to a distant metastasis or to extension to a neighboring organ. This was true in 32.6 per cent of 46 clinical cases and in 50 per cent of 46 autopsy cases herein reviewed.

Such a metastasis or extension may mimic a neoplasm of the bone, pulmonary disease, a lesion of the brain, spinal cord or peripheral nerves, cirrhosis of the liver, a lesion of the stomach or colon or a tumor of the neck, or it may cause unexplained anemia, fever or cutaneous lesions. It may also cause confusion with other diseases of the urinary tract (renal stones, vesical tumors, perinephric abscess) or be masked by them (stones). The primary tumor may be mistaken for an ovarian cyst.

Confusion may at times be avoided by a painstaking eliciting of the history and by a careful physical examination; the lesions are best recognized in obscure cases if one bears in mind the possibility of a renal tumor and excludes that diagnosis by intravenous urograms supplemented, as is often necessary, by retrograde pyelograms.

There was no instance of solitary bony metastasis in this group, although such a metastasis occasionally occurs and may be amenable to surgical intervention.

Thirty-six different organs—counting the bones as one organ system—were involved by metastasis in 92 cases of malignant renal neoplasm here reviewed. Twelve different bones were affected.

Since this article was written, three additional unusual instances of hypernephroma have been seen at the University Hospitals.

The first was the case of a woman, aged 39, who had been treated for several months in the outpatient department because of low grade fever, occasional rigors, generalized pain, and anemia (the hemoglobin was from 43 to 55 per cent). Because of a history of exposure, an agglutination titer at first of 1:80 and later of 1:320 for *Brucella abortus* and a positive Foshay cutaneous test, a diagnosis of undulant fever was made. Treatment with Foshay's vaccine produced no improvement, but chills, fever and loss of weight continued. The patient died after a series of convulsive seizures recurring over a period of several weeks.



Autopsy showed a necrotic hypernephroma of the right kidney without metastasis. The brain and meninges were normal. There was some proliferation of the reticulo-endothelial cells of the liver and spleen.

It is interesting but rather fruitless to speculate as to the relative rôles of the renal neoplasm and the undulant fever in producing the fatal outcome.

The second case was that of a man, aged 64, with a history of cough of three years' duration without impairment of the general health. Two months before admission there was hemoptysis followed by the coughing up of a "piece of flesh." This was examined by a pathologist who said that it resembled a papilloma. Later another piece was coughed up, and the tissue was diagnosed as carcinoma of undetermined origin. Roentgen examination of the chest showed an irregular infiltration extending from the hilus of the right lung and suggesting a bronchogenic carcinoma. Bronchoscopy was made with negative results. The patient then had hematuria for the first time and was hospitalized for pyelography. There had never been any other urinary symptoms. The pyelograms showed a typical neoplasm of the right kidney. Reexamination of the sections of the second coughed up specimen showed it to have an appearance consistent with that of hypernephroma.

The third case was that of a man, aged 49, who consulted his physician in April 1934 because of loss of weight and strength. Examination showed pleural effusion on the left side, and the patient was sent to a sanatorium. He was discharged after five months, much improved and classed as nontuberculous. Three months later weakness of the left arm developed, which was followed by attacks of jacksonian epilepsy. The patient was then admitted to the University Hospital, a tumor of the right frontal lobe was suspected. Roentgenograms of the lungs demonstrated nodular metastases. The right kidney was found to be nodular and enlarged, excretory urography showed a picture typical of renal neoplasm.

# ALTERATIONS OF THE ELECTROCARDIOGRAM IN DISEASES OF THE PERICARDIUM

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In the voluminous literature on electrocardiography comparatively little space has been devoted to the electrocardiographic findings in diseases of the pericardium. The mechanism of the production of these alterations has interested us. Recently<sup>1</sup> attention has been directed to the similarity of the changes occurring in the RS-T segment of the electrocardiogram in cases of pericardial involvement with an accumulation of fluid in the sac and those seen in the early stages of acute closure of a coronary artery. We have been able to find only one reference<sup>2</sup> in the clinical literature to the changes in the T wave occurring in diseases of the pericardium. Serial electrocardiographic studies, such as we have made, have not been previously carried out in the various stages of pericardial involvement, and this accounts, in a measure, for the paucity of data concerning the abnormalities appearing during inflammation, effusion, reabsorption and healing of the processes. We have been able to show that the electrocardiographic analogy that exists between acute pericardial processes and coronary thrombosis with cardiac infarction not only occurs at the time of the acute stage but continues through the periods of healing and repair. Elevations of the RS-T sector or "high take-offs" occurring in cases of acute pericardial effusion and hemopericardium are followed by progressive changes in the T wave which simulate, in most respects, the changes occurring in cases of acute and healing myocardial infarctions. At this point it is to be emphasized that similar abnormalities of the T wave may occur in cases of acute fibrinous pericarditis, irrespective of etiology, without an accompanying effusion and without preceding changes in the RS-T segment. As the clinical pictures of pericardial processes and coronary thrombosis with myocardial infarction may also so closely mimic one another, it behooves one to bend every effort to establish

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1 Scott, R. W., Feil, H. S., and Katz, L. N. The Electrocardiogram in Pericardial Effusion. *Clinical, Am Heart J* 5:68 (Oct) 1929

2 Porte, D., and Pardee, H. E. B. The Occurrence of Coronary T-Wave in Rheumatic Pericarditis, *Am Heart J* 4:584 (June) 1929

differences in the electrocardiogram in the two conditions. To this end a careful comparative analysis of the serial electrocardiograms in our own series of cases together with those found in the literature has been undertaken.

#### REVIEW OF THE LITERATURE

The literature on the electrocardiographic findings in cases of pericarditis has accumulated in the last decade. In 1923 Oppenheimer and Mann<sup>3</sup> reported as significant findings a striking decrease in the voltage of the electrocardiograms of seven patients with pericardial effusion. No electrocardiograms were published. Scherf<sup>4</sup> later pointed out similar observations in 1926, but he did not publish his curves until 1930. Cohn and Swift,<sup>5</sup> in 1924, reported the occurrence of changes in the T wave in patients with rheumatic fever which they considered evidence of myocardial involvement. Further study of their three plates revealed that the patient whose electrocardiograms made up plate I had had precordial pain, while the patient whose electrocardiograms were shown in plate II had had a definite pericardial friction rub, unfortunately, there was no clinical history to go with plate III. In the first case slight changes occurred in the RS-T sector and T wave in leads II and III. A small inconspicuous Q wave was present in those leads, which, however, showed no change in size or configuration throughout the illness. In the second instance, definite deviations in the RS-T sector with a paradoxical relationship in leads I and III were apparent, and these were followed eighteen days later by negativity of the T wave in lead I. The significance of these observations is minimized owing to the fact that digitalis had been administered. There were no Q waves.

Gager,<sup>6</sup> in 1924, reported a case of pericardial effusion of uncertain etiology in a patient with organic heart disease and emphasized the disturbance in auriculoventricular conduction time. In addition, the electrocardiogram showed a decrease in voltage, changes in the RS-T segment with a paradoxical relationship in leads I and III, and abnormalities of the Q wave as well as of the T wave. An additional curve taken immediately following the removal of 500 cc of exudate showed disappearance of the auriculoventricular block and the alterations of the RS-T segment and an increase in voltage. Subsequent curves taken

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3 Oppenheimer, B. S., and Mann, Hubert. An Electrocardiographic Sign in Pericardial Effusion, *Proc Soc Exper Biol & Med* **20** 431, 1923.

4 Scherf, D. Ein elektrokardiographisches Zeichen bei Erguss im Herzbeutel, *Wien klin Wchnschr* **43** 298 (March 6) 1930, *Wien med Wchnschr* **7** 226, 1927.

5 Cohn, A. E., and Swift, H. F. Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J Exper Med* **39** 1 (Jan) 1924.

6 Gager, L. T. Conduction Changes Accompanying Pericardial Effusion with a Consideration of a Local Circulatory Factor in Heart Block, *Arch Int Med* **33** 449 (April) 1924.

eighteen and twenty-two months after the onset revealed a progression of the inversion of the T wave and a gradual increase in the depth of the Q waves which were originally present.

In the series of patients with uremia and severe chronic nephritis studied by Wood and White,<sup>7</sup> the cases of two with a complicating pericarditis were presented with their electrocardiograms. In one instance (case 2) pericardial effusion was the terminal event, and an electrocardiogram taken four days before death revealed a marked positive deviation of the RS-T segment from the iso-electric level in leads I and II and slight deviation in lead III. The authors concluded that the toxic effect of uremia on the cardiac muscle was the most likely explanation of the rapidly changing electrocardiographic complexes. In the other case (case 3), acute pericarditis was noted at autopsy. The electrocardiogram taken the day before death showed slight elevation of the RS-T segment above the iso-electric level in lead I, and all the T waves were increased in amplitude, with sharpened apices similar to those which we have encountered in the electrocardiograms of goats with experimental pericarditis.<sup>8</sup> There were no significant changes in the Q wave in either case.

Porte and Pardee,<sup>2</sup> in a study of three cases of acute rheumatic pericarditis, called attention to the finding of "coronary T waves" in the presence of this disease. They did not consider the possibility that the pericardial involvement accounted for the electrocardiographic changes and attributed them to a complicating myocardial inflammatory reaction. In all instances there were negativity of the T waves and upwardly convex RS-T sectors in the significant leads. There were no Q waves apparent in any of the cases. In their third case, a curve taken two months after recovery revealed a disappearance of the abnormalities of the T wave previously present.

Scott, Feil and Katz<sup>1</sup> reported changes in the RS-T segment of the ventricular complexes in three cases of pericardial involvement. In the first case, one of hemopericardium resulting from a ruptured aneurysm, there was a striking positive deviation of the RS-T sector in all three leads. Thirty-three days later the abnormalities of the RS-T sector had practically disappeared and T<sub>1</sub> was diphasic, with inverted T<sub>2</sub> and T<sub>3</sub>. The latter changes were not commented on. At autopsy both the visceral and the parietal layer of the pericardium

7 Wood, J. F., Jr., and White, P. D. The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, *Am. J. Med. Sci.* **160**: 76 (Jan.) 1925.

8 Herrmann, G. R., and Schwab, F. H. Some Experimental and Clinical Electrocardiographic Observations on RS-T and T Changes in Pericarditis, *Tr. A. Am. Phys.* **40**: 229, 1934. Herrmann, G. R., Williams, H., and Williams, D. *Proc. Soc. Exper. Biol. & Med.* **31**: 1050, 1934.

were greatly thickened and were covered by a partially organized blood clot. The second case was one of suppuration in the pericardial sac, and the curves displayed similar but not as prominent abnormalities of the RS-T segment, with a small  $Q_2$  and a more pronounced  $Q_3$ . The last case was one in which rheumatic pericardial effusion was suspected, but not proved. There was a positive elevation of the RS-T sector in all three leads, which disappeared nineteen days later. At that time a flattened T wave was present in all leads. In the initial curve an inconspicuous Q wave in leads I and II was noted, which was not present in the final electrocardiogram. These observers attributed the abnormalities of the RS-T segment to an anoxemic state of the cardiac muscle resulting from the increased hydrostatic pressure within the pericardial sac.

The electrocardiograms in Scherf's<sup>4</sup> case showed low voltage of the complexes in all leads. Following aspiration, an increase in amplitude of the waves occurred and, in addition, negativity of the T wave in leads II and III, the latter finding disappeared some time later. There were no Q waves.

Agostoni and Papp<sup>9</sup> recorded two cases of rheumatic pericardial effusion with electrocardiographic studies. Both cases were unusual in that they showed auriculoventricular as well as bundle branch conduction disturbances, the latter finding invalidating to a certain extent the T wave changes present. Rather prominent Q waves were present in the first case and persisted. In the second instance a Q wave was present in lead III.

In the electrocardiograms in the case of pyopericardium studied by Harvey and Scott,<sup>10</sup> there was a high take-off of the RS-T segment in all leads, but it was more pronounced in leads I and II. Following repeated aspiration and finally surgical drainage, the changes nearly disappeared. There was a gradual and pronounced decrease in the voltage of the T wave. An inconspicuous Q wave persisted in leads II and III.

An additional case of purulent pericarditis with electrocardiographic study was reported by Purks.<sup>11</sup> The single electrocardiogram revealed a marked positive deviation of the RS-T sector in all leads with slight negativity of the T wave in leads I and II and an iso-electric  $T_3$ . There

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9 Agostoni, G., and Papp, C. Gibt es elektrokardiographische Zeichen bei Herzbeutelerguss? *Wien klin Wchnschr* **43** 842 (July 3) 1927.

10 Harvey, J., and Scott, J. W. Changes in the Electrocardiogram in Course of Pericardial Effusion with Paracentesis and Pericardiotomy, *Am Heart J* **7** 532 (April) 1932.

11 Purks, W. K. The Occurrence of a Coronary T-Wave in Purulent Pericarditis, *South M J* **24** 1032 (Dec) 1931.

were no Q waves. At necropsy the pericardial sac contained about a liter of pus, and the myocardium subjacent to the visceral pericardium showed an inflammatory reaction.

#### REPORT OF CASES

The case histories and serial electrocardiographic studies of seven cases of pericardial disease are presented. In six cases fluid of some type was present in the pericardial sac. The etiologic factor was rheumatic fever in two instances, tuberculosis in one and streptococcic suppuration in one, there was one case of polyonchococcal Pick's disease and one of hemopericardium following a gunshot wound. There was one case of acute fibrinous pericarditis without effusion of streptococcic origin. The majority of the cases were in young persons, and in each instance the presence of organic heart disease and recognizable pathologic processes of the coronary arteries could be definitely excluded.

**CASE 1—History**—W. R., a Negro, aged 48, was first seen in the outpatient department of the John Sealy Hospital on Feb. 26, 1932, with the complaint of a sore throat. Examination revealed an acutely inflamed pharynx. The temperature was 101 F. The condition was treated locally, and the patient was advised to return the following day. He was not seen again until February 29, when he stated that his condition had become progressively worse. The fever had increased, and pain had developed in the left side of the chest. A slight cough with scanty expectoration had appeared. It was felt that hospitalization was necessary.

The past history was inconsequential. The patient said that he had never had a venereal infection. The family history revealed that his parents were both living, aged 85 and 80, respectively.

**Examination**—Physical examination showed a man who appeared older than the stated age of 48 years and who was acutely ill. His temperature was 103 F., the pulse rate was 124, and the respirations numbered 26 per minute. The throat was acutely inflamed and edematous, and at the base of the uvula there was a necrotic ulcer. The cervical glands at the angle of the jaws were enlarged and tender. Diminished expansion over the base of the left lung was apparent, and posteriorly crepitant and subcrepitant rales were heard. The area of cardiac dullness was found to be slightly increased by percussion. The heart sounds were well heard, and no murmurs or other adventitious sounds were present. The blood pressure was 130 mm. of mercury systolic and 95 diastolic. The pulse rate was rapid and regular. The radial arteries were moderately thickened. Abdominal examination revealed no areas of tenderness, and the liver and spleen were not palpable.

Examination of the urine gave negative results except for a few hyaline casts. The hemoglobin content was 75 per cent, the red blood cells numbered 3,460,000 per cubic millimeter, and the white blood cells, 3,350, with essentially a normal differential count. The complement-fixation test for syphilis was negative. A smear from the throat was negative for diphtheria but showed many short chain streptococci.

**Progress**—The patient failed to improve under treatment. Dyspnea and precordial pain became prominent symptoms. On March 4, a pericardial effusion was suspected and confirmed by roentgenographic study. On this date auricular

fibrillation with a rapid ventricular rate appeared. On March 5, material was aspirated from the pericardium, and a thick, purulent exudate was obtained, which on culture yielded a rich growth of short chain streptococci. The leukocytes rose to 15,000 per cubic millimeter, with 86 per cent granular forms. A Schilling count revealed a 25 per cent shift to the left. Large doses of digitalis failed to control the auricular fibrillation. The pericardium was again aspirated on March 8, a similar exudate being obtained. The patient's condition rapidly became worse, and death occurred on March 9.

*Necropsy*—From the pericardium was obtained about 800 cc of a greenish-gray purulent material containing large amounts of fibrin. The heart was covered with a shaggy coat of this material and weighed 300 Gm. No significant valvular lesions were noted. The coronary arteries were remarkably free from sclerotic

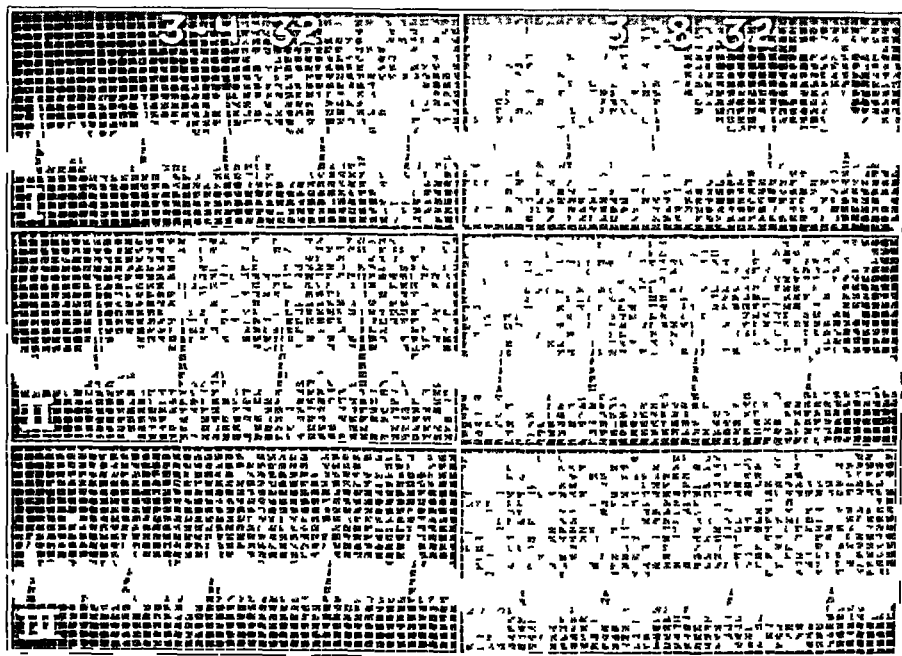


Fig 1 (case 1)—Electrocardiograms in a fatal case of acute purulent streptococcic pericarditis following a streptococcic sore throat. The gradual accumulation of fluid in the pericardial sac was evidenced by serial teleoroentgenograms which showed 22 per cent enlargement on March 4, 25 per cent on March 5 and 32 per cent on March 7. Descriptions of these and subsequent electrocardiograms are found in the text.

changes. Marked hypostatic pneumonia was present. The liver, spleen and kidneys showed considerable cloudy swelling.

Acute purulent streptococcic pericarditis was the evident diagnosis.

*Electrocardiograms*—Unfortunately only two electrocardiograms were taken, both after the advent of auricular fibrillation (fig 1). The first, taken on March 4, before the administration of digitalis, showed a slight elevation of the RS-T sector in leads I and II,  $T_3$  was sharply inverted. Rather marked slurring of the QRS complex was present in all leads. Four days later the RS-T segments had returned to the iso-electric levels.  $T_1$  was flattened, and  $T_2$  and  $T_3$  had become sharply inverted and were preceded by an upward convexity of the ST interval.

There were no Q waves. In view of the administration of digitalis in this case, the significance of the changes in the T wave is open to question. It may be said, however, that they do not conform to the type generally found following digitalization.

*CASE 2—History*—A D, a senior medical student, aged 26, was admitted to the John Sealy Hospital on March 21, 1932, with the complaint of general malaise, weakness and fever. One week before admission he had acute nasopharyngitis associated with a severe sore throat. The latter condition was treated locally, and all symptoms disappeared in about three days. Two days later he began to feel weak and dizzy, lost his appetite and felt as if he had fever. On the day of admission, while sitting in class, he chanced to place his hand over the precordium and immediately recognized the presence of a pericardial friction rub. There had been no pain.

The patient's past history did not reveal tonsillitis or any manifestation of rheumatic fever or chorea. At the age of 10 years he had suffered an attack of influenza, which was mild. There was no history of any venereal disease. The family history was irrelevant.

*Examination*—Physical examination revealed a well nourished young man who did not appear acutely ill. His temperature was 100.4 F, the pulse rate was 96, and the respiratory rate was 20. The tonsils were small, but along with the pharynx showed a mild hyperemia. The cervical glands were not enlarged. On palpation over the precordium a definite friction fremitus was noted. The heart was normal in size on percussion. On auscultation a loud, harsh, grating friction rub was heard. There were no murmurs. The blood pressure was 135 mm of mercury systolic and 85 diastolic. Examination of the chest gave entirely negative results. No tenderness was present in the abdomen, and the liver and spleen were not palpable.

Laboratory examinations showed a hemoglobin content of 82 per cent, a red blood cell count of 3,880,000 and leukocytosis, the white blood cell count being 15,150 with 73 per cent polymorphonuclear forms. The urine was normal.

A teleoroentgenogram revealed a heart of normal size and configuration.

A diagnosis of acute fibrinous pericarditis of probable rheumatic streptococcic origin seemed justifiable.

*Progress*—A low grade fever with the peaks of temperature reaching 100 F persisted for eight days. The friction rub gradually became less intense and disappeared at about the same time that the temperature returned to normal. Repeated roentgenographic studies failed to demonstrate, at any time, any evidences of increased fluid in the pericardial sac. A sinus tachycardia persisted for several weeks.

The patient was discharged on May 29, apparently completely recovered. He has returned at intervals for follow-up studies, and at no time have any evidences of heart disease been found.

*Electrocardiograms*—The electrocardiograms are shown in figure 2. The initial curve, on March 21, revealed low voltage of the QRS complex in all leads, with marked slurring. T<sub>1</sub> and T<sub>2</sub> were upright but of low voltage, and T<sub>3</sub> was iso-electric. One week later, on March 28, T<sub>1</sub> had become sharply inverted and was preceded by an upward convexity of the RS-T segment. Associated with this change there was an increase in the voltage of T<sub>1</sub>. On April 6, T<sub>2</sub> had assumed a configuration similar to that in lead I. On April 20, T<sub>1</sub> and T<sub>2</sub> had again become upright but were of low voltage. On subsequent curves the voltage



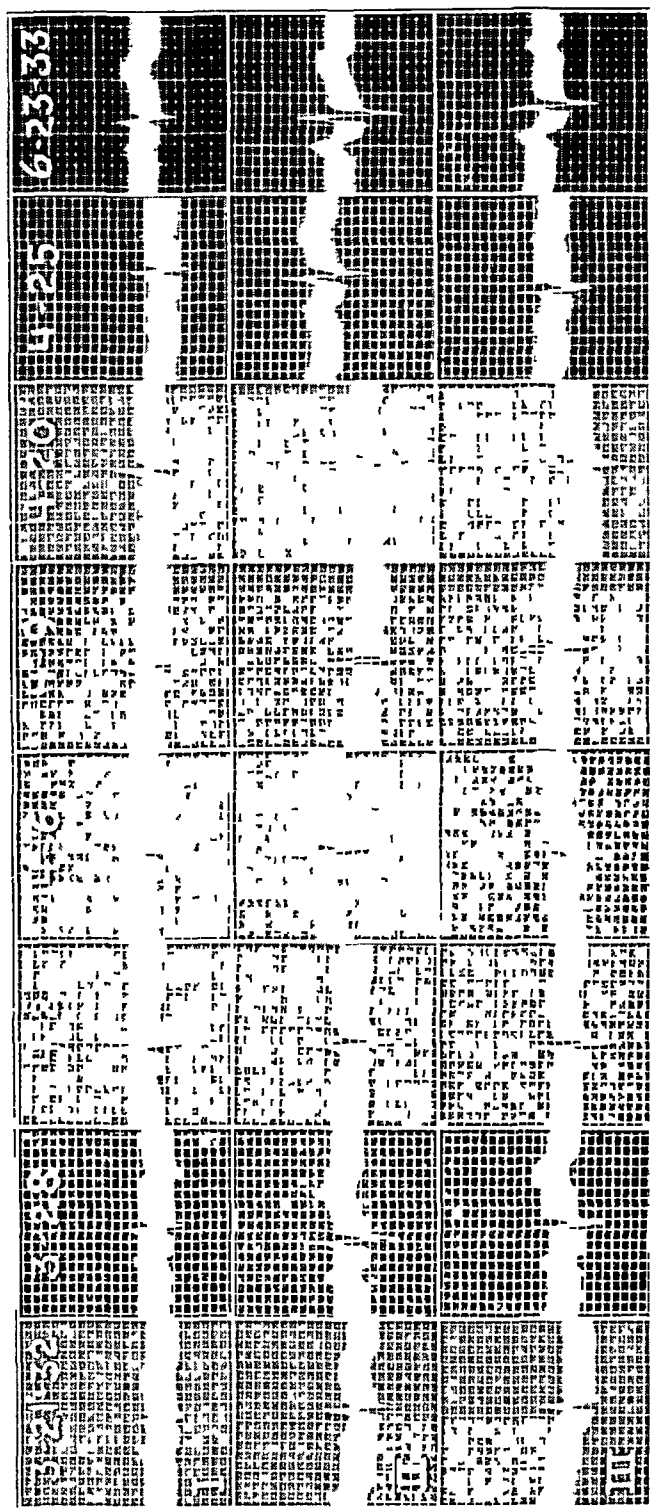


Fig 2 (case 2) —Electrocardiograms in a case of acute fibrinous pericarditis without effusion of probable rheumatic origin with complete recovery

of the T waves increased Throughout the course of the illness there was no definite change in the voltage and configuration of the QRS complex The last curve, taken on June 23, 1933, did, however, show a slight increase in voltage of the ventricular complex At no time was there any deviation of the RS-T segment from the iso-electric level No Q waves appeared

CASE 3—*History*—D S., a white man, aged 22, was admitted to the John Sealy Hospital on Jan 11, 1932, because of shortness of breath and pain in the chest He had not been in good health for several months because of repeated respiratory infections He first noticed pain in the lower portion of the left side of the chest two weeks prior to admission This pain was evanescent, but gradually increased in intensity Fever was noticed at times, but it was not thought to be high On January 8, the patient had a severe chill followed by high fever That night he became very short of breath and spent the greater part of the night in the sitting position The pain increased in intensity A severe cough developed with the expectoration of blood-streaked sputum He had had little appetite and had lost between 5 and 10 pounds (2.3 and 4.5 Kg) in weight during the past few weeks

In childhood he had had measles, mumps and chickenpox Pneumonia in 1926 was followed by an attack of acute rheumatic fever which lasted for five weeks In September 1931, he had a penile chancre, which had not completely healed when he came to the hospital The family history was inconsequential

*Examination*—Physical examination showed an acutely ill young man who was in considerable respiratory distress His temperature was 102 F, the pulse rate was 110, and the respiratory rate was 20 per minute Slight cyanosis of the forehead, lips and cheeks was present There was no maculopapular rash on the skin No mucous patches could be found in the mouth The tonsils were small and embedded A moderate amount of pyorrhea alveolaris was present The chest was of normal size The respiratory excursion was decreased over the posterior aspect of the left side of the chest below the angle of the scapula, and there were increased tactile fremitus, dullness on percussion, bronchial breathing and bronchophony No rales were heard

There was slight prominence of the precordium The apex impulse was neither visible nor palpable The area of cardiac dullness was increased both to the right and to the left On auscultation over the precordium a loud, leathery pericardial friction rub was heard The pulse was easily compressible and regular, had a rate of 108 per minute and was not paradoxical The blood pressure was 110 mm of mercury systolic and 78 diastolic Considerable tenderness was encountered in attempted palpation of the upper part of the abdomen The liver and spleen were not palpable None of the joints of the body showed evidence of disease On the undersurface of the glans penis, a raised, ulcerated area was present, which appeared to be healing There was no edema of the extremities

Examination of the urine gave negative results The hemoglobin content was 64 per cent, the red blood cells numbered 3,610,000 per cubic millimeter, and the white blood cells, 13,200, with 66 per cent polymorphonuclear forms The complement-fixation and precipitation tests for syphilis were strongly positive The blood culture was negative A teleoroentgenogram taken on admission revealed evidence of a moderate degree of pericardial effusion

*Progress*—With complete rest in bed and the administration of salicylates, the patient's condition gradually improved The friction rub progressively became less intense and disappeared on the eighth day along with the fever A teleoroentgenogram taken on January 22 showed a considerable decrease in the size of

the cardiac shadow, and on January 29 the fluid had apparently been entirely reabsorbed and the heart was reported to be normal in size and configuration. Recovery from the pericarditis was rapid and complete, and the patient was discharged on February 10. Cardiovascular examination at that time revealed no abnormalities.

Acute syphilitic pericarditis is a rare condition, and the previous history, together with the high fever, leukocytosis and response to salicylates, seems to establish the diagnosis of acute rheumatic pericarditis with effusion.

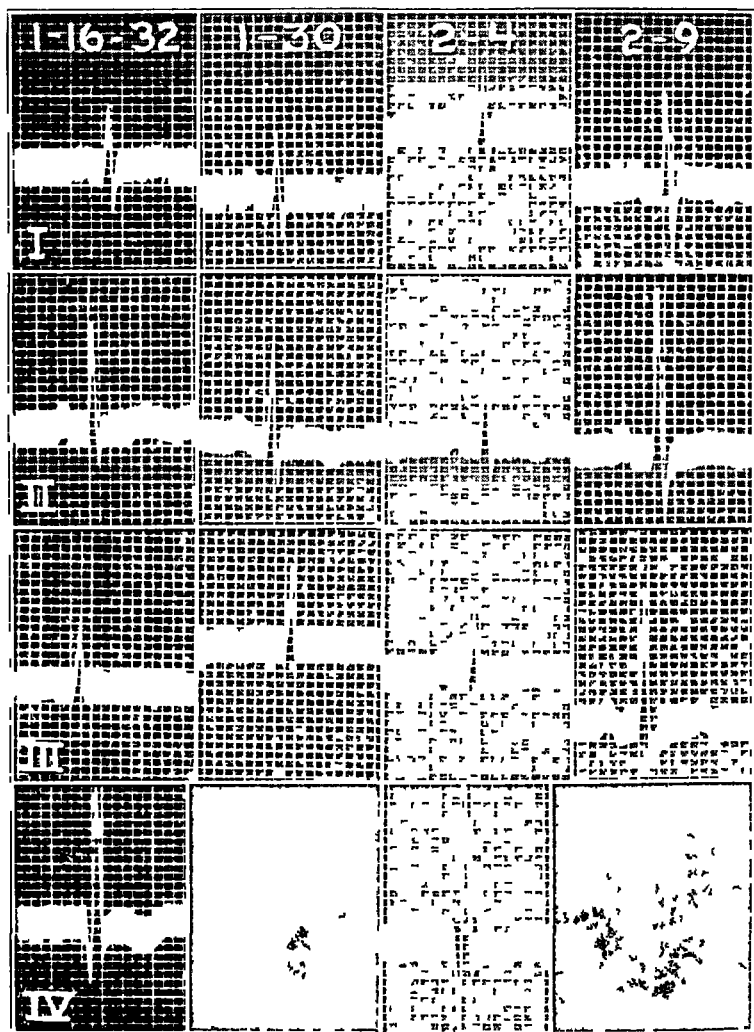


Fig 3 (case 3)—Electrocardiograms in a case of acute rheumatic serofibrinous pericarditis. Teleoroentgenograms taken on January 12 revealed 32 per cent enlargement of the cardiac shadow, on January 22, 20 per cent enlargement, and on January 29, a cardiac silhouette of normal size and configuration.

*Electrocardiograms*—The electrocardiograms are shown in figure 3. In this case, although an effusion was definitely present, no abnormalities of the RS-T segment were noted. The initial electrocardiogram, taken on January 16, was essentially normal except for the low voltage of the T wave in all leads. Lead IV, however, was considered as being abnormal. Two weeks later, January 30, inversion of the T wave was present in all leads, particularly in derivations I and

II, along with an upward convexity of the RS-T sector. Five days later, on February 4, this change was still present with the exception that T<sub>2</sub> had become positive. The last curve, taken on February 9, revealed an upright T<sub>2</sub> and T<sub>3</sub>, T<sub>1</sub> still being definitely inverted. Electrocardiograms taken in three positions at that time revealed some fixation of the electrical axis, but it was not complete. Unfortunately, the patient could not be followed and no further electrocardiographic studies were made. There were no Q waves.

**CASE 4—History**—W. D., a white fisherman, aged 32, entered the John Sealy Hospital on Jan. 12, 1932, because of pain in the chest and shortness of breath. He dated his illness from Dec. 4, 1931, when he first noticed an aching pain beneath the upper portion of the sternum which radiated upward to the left shoulder and posteriorly to the left scapula. This pain was made worse by stooping, changing position, coughing or deep breathing. At the same time the patient began to notice some shortness of breath. This seemed to disturb him most when he was lying down, especially at night after going to bed. To get relief he would have to sit up in bed. These symptoms persisted for three days and then disappeared.

About December 24, while tonguing oysters, he again became short of breath. The pain in the chest reappeared soon thereafter. This attack, of the same character, came on and gradually increased in severity, finally causing him to come to the hospital. A troublesome dry, hacking cough was present. Fever had been present for several days. A roentgenogram of the chest taken on January 9 revealed no abnormality.

Each winter for many years the patient had had many respiratory infections. In 1927 he was operated on for an abscess of the abdominal wall. In 1910 he had a penile chancre, followed by a cutaneous eruption, for which he received a negligible amount of therapy. During childhood he had had mumps, whooping cough and bloody diarrhea, the last-mentioned condition recurring at irregular intervals ever since. The family history was inconsequential.

**Examination**—Physical examination showed a white man of about the stated age of 32, who appeared to be in considerable pain and respiratory distress. The cervical veins were abnormally distended. The mouth and pharynx were in a poor hygienic state. Examination of the chest gave negative results except for the physical signs indicating compression of the base of the left lung posteriorly. Palpation of the precordium revealed a faint friction fremitus. On percussion the area of cardiac dullness was increased both to the right and to the left, and the configuration was definitely altered by changes in position. On auscultation a loud to-and-fro friction rub was heard over the third and fourth left intercostal spaces, synchronous with heart action. The heart sounds were of fair quality but distant. The pulse rate was 100, the rhythm was regular. The blood pressure was 116 mm. of mercury systolic and 74 diastolic. The peripheral arteries showed no sclerosis. The edge of the liver was felt just below the costal margin. The spleen was not palpable. An indolent ulcer was present on the anterior aspect of the left leg.

Examination of the urine gave negative results. The hemoglobin content was 76 per cent, the red blood cell count was 4,250,000 per cubic millimeter, and the white blood cells numbered 10,400, with 55 per cent polymorphonuclear forms. Complement-fixation and precipitation tests for syphilis were negative. Examination of the stool failed to reveal *Endamoeba histolytica*. A teleoroentgenogram taken on January 12 revealed the presence of a pericardial effusion.

**Progress**—Intermittent fever was present for eight days, the peaks of temperature being around 103 F., with a corresponding increase in the pulse and respira-

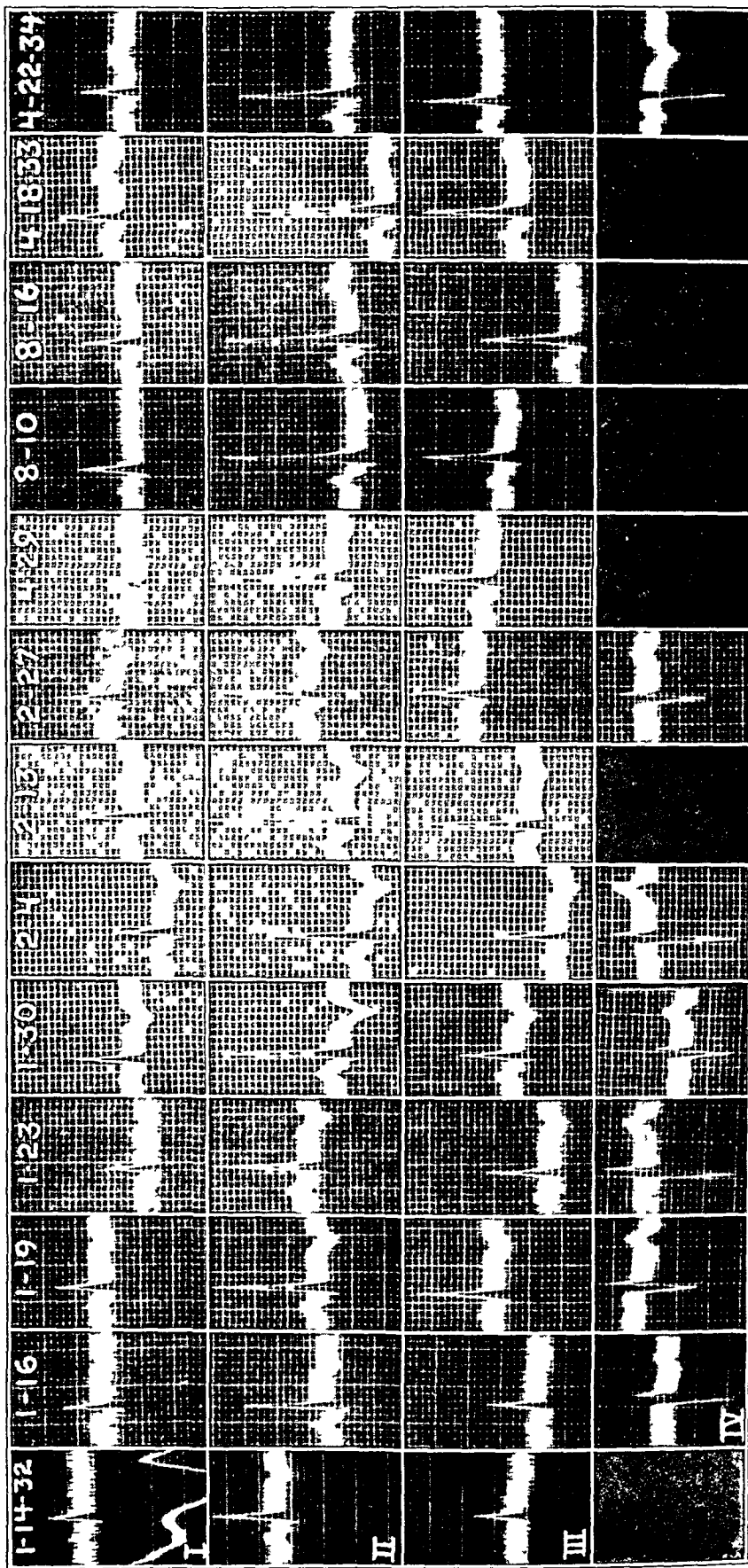


Fig 4 (case 4) —Electrocardiograms in a case of acute and subacute serofibrinous pericarditis of rheumatic origin. Teleoroentgenograms taken on January 12 revealed 33 per cent enlargement of the cardiac shadow, on January 13, 49 per cent enlargement, and on January 22, 5 per cent

tory rates. On the fifth day of salicylate therapy the symptoms began to subside. A teleroentgenogram taken on January 22 showed that the pericardial effusion had been reabsorbed and that the size and configuration of the heart were normal. Recovery was uninterrupted, and the patient was discharged on March 1. He has been seen on several occasions since that time and has had no recurrence of symptoms or signs.

The diagnosis of acute rheumatic pericarditis with effusion seemed to be warranted.

*Electrocardiograms*—The numerous electrocardiographic studies made and the date on which each was taken are depicted in figure 4. In the first two electrocardiograms, taken on January 14 and 16, there was a definite elevation of the RS-T segment above the iso-electric level in the three conventional leads, terminating in a negative T wave. Lead IV on January 16 similarly showed deviation of the RS-T sector. With the disappearance of the accumulation of fluid in the pericardial sac there was a return of the RS-T segment to the base line, and coincidentally, the degree of negativity of the T wave became more marked and the voltage of the QRS complex increased. Coincident with the inversion of the T wave in the usual leads, there was an increasing degree of positivity in the anteroposterior chest lead. On February 13 the inverted T wave was preceded by a well defined upward convexity of the RS-T interval in all leads. Three and one-half months after the onset of the illness  $T_1$  had become positive but was low in voltage. Subsequently, on August 16,  $T_1$  had increased in voltage and  $T_2$  had become upright, although  $T_3$  remained inverted. Curves taken approximately eight, sixteen and twenty-four months later showed that the condition had become stationary as no further significant changes were observed. Electrocardiograms taken in three positions on Feb. 13 and Aug. 16, 1932, and April 22, 1934, showed no fixation of the electrical axis. In the initial electrocardiograms a Q wave was present in leads I and II, and later this wave appeared in lead III. Its depth and configuration were similar to those encountered in many normal curves, and, furthermore, no significant changes in this component of the ventricular complex occurred throughout the period of study.

*CASE 5—History*—G. W., a Negro laborer, aged 33, was admitted to the John Sealy Hospital on Feb. 24, 1933, because of shortness of breath and weakness. Seven weeks before entry he began to have night sweats. About a week later he noticed that he became short of breath after mild exertion and that his heart would beat very fast. He suffered no actual pain, but at times he had a sense of oppression in the left side of the chest. He thought that he had had fever every night since the sweats began, but he had not used a thermometer. On arising in the morning he usually coughed some, expectorating a mucopurulent sputum. He had never coughed up or expectorated blood. There had been a loss of weight of 6 pounds (2.7 Kg.), although the appetite had remained good.

In June 1932, he had an attack of acute appendicitis. Operation was advised, but he refused and the condition subsided. During 1927 he was under treatment several weeks in the outpatient department for a right pleural effusion, which was apparently reabsorbed. During the winter of 1926 he was hospitalized a few days because of a severe attack of bronchitis. In the same year he contracted gonorrhea, for which he was treated six months. At this time there was present also a penile sore which was cauterized. During childhood he had measles, whooping cough, mumps and "chills and fever." The family history was irrelevant.

*Examination*—Physical examination revealed a well nourished Negro of about the stated age of 33, who did not appear acutely ill. His temperature was 99 F.,

his pulse rate was 90 per minute and his respiratory rate 20. The pupils were equal and reacted to light and in accommodation. The sclerae showed no icterus. The tonsils were small and innocent in appearance. There were no palpable cervical glands. The chest was of the sthenic type. Slight dullness on percussion was present in the base of the left lung. There were no changes in the breath or the voice sounds, and no adventitious sounds were heard.

Palpation of the precordium gave negative results. On percussion the area of cardiac dullness was considerably enlarged in all directions. A definite change in the size of the area of retromanubrial dullness was noted when the patient assumed the upright position. On auscultation a definite pericardial friction rub was heard in the third and fourth interspaces to the left of the sternum. The heart sounds were of fair quality and intensity. The aortic second sound was

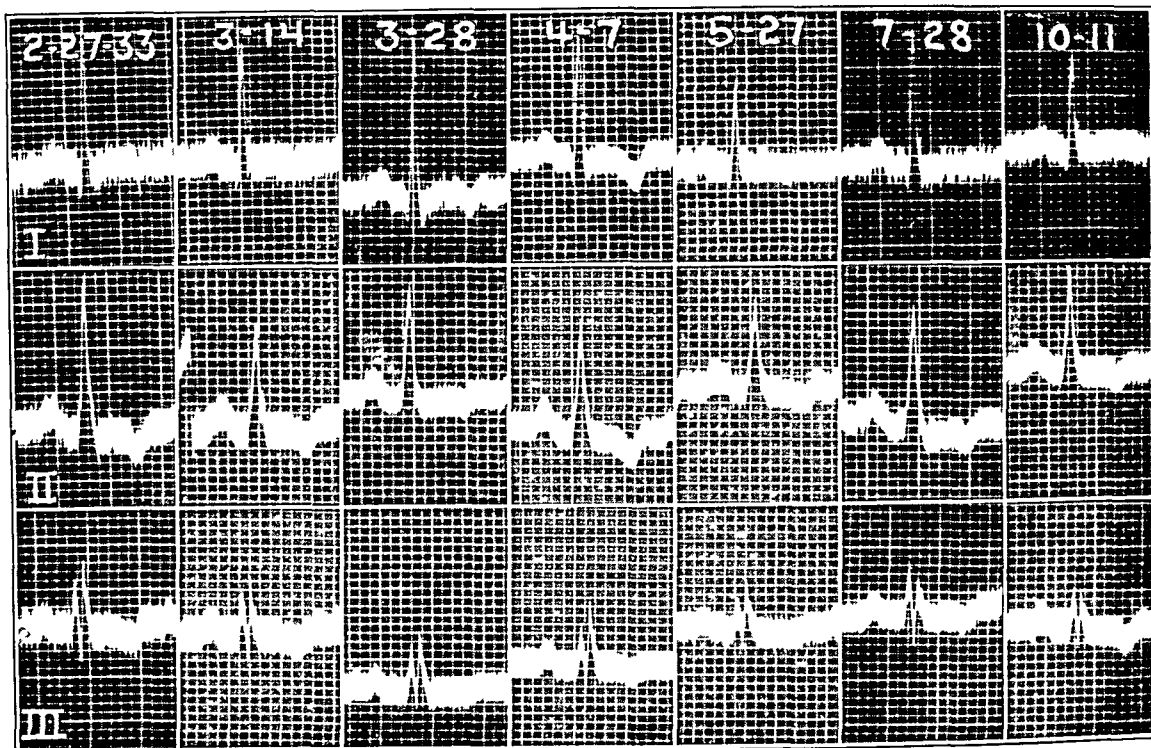


Fig 5 (case 5)—Electrocardiograms in a case of subacute to chronic sero-fibrinous pericarditis of tuberculous origin. The degree of enlargement of the cardiac shadow shown by the roentgenogram was 22 per cent on February 25, 26 per cent on March 18 and 15 per cent on April 17.

moderately accentuated. No murmurs were heard. The pulse rate was 90 per minute, and the rhythm was regular. The blood pressure was 124 mm of mercury systolic and 90 diastolic in both arms. The liver was just palpable below the costal margin but was not tender. The spleen could not be felt. There was no edema of the extremities.

Examination of the urine revealed a trace of albumin. The hemoglobin content was 80 per cent, the red blood cells numbered 4,680,000 per cubic millimeter, and the white blood cells, 4,200, with an essentially normal differential count. The complement-fixation and precipitation tests for syphilis were negative.

A teleoroentgenogram taken on admission showed a marked increase in the cardiac measurements, although the configuration was not typical of that of a pericardial effusion. A diagnostic paracentesis was not done, but in view of the fact that subsequent roentgenographic studies revealed a considerable decrease in the size of the shadow, it seems logical to conclude that a pericardial effusion had been present.

*Progress*—Low grade fever was present for the first week, the temperature never exceeding 100 F. The pulse rate remained elevated after the temperature returned to normal. On the sixth day the pericardial friction rub disappeared. A teleoroentgenogram taken on March 18 showed a decrease in the cardiac measurements, and another taken on April 17 revealed a further reduction in size and a heart shadow which was essentially normal in outline. The patient's condition improved rapidly. He gained 17 pounds (7.7 Kg) in weight and was discharged from the hospital on April 28. He has been seen on several occasions since that time and has remained well.

The diagnosis of acute tuberculous pericarditis with effusion seems to be justifiable.

*Electrocardiograms*—The electrocardiogram taken on admission (fig 5) revealed a T wave of low voltage in lead I with sharp inversion in leads II and III. In leads II and III a slight upward convexity of the RS-T segment was present, but otherwise there was no deviation from the iso-electric level. The significant changes in subsequent electrocardiograms occurred in lead I, little change taking place in leads II and III. On March 14, the first evidence of negativity of  $T_1$  appeared. Two weeks later the final deflection in lead I was sharply inverted and preceded by a marked convexity of the RS-T interval, originating on the iso-electric line. This degree of negativity of  $T_1$  increased for a time and then gradually became less, and the curve taken on July 28 revealed a flat  $T_1$ . In the electrocardiogram taken on November 11,  $T_1$  had become positive but was of low voltage. Electrocardiograms taken in three positions on March 1, 1934, revealed practically complete fixation of the electrical axis. No significant Q waves appeared.

*CASE 6—History*—L. C., a Negro laborer, aged 24, was first admitted to the John Sealy Hospital on April 11, 1932, because of pain in the chest. He dated his illness from March 30, 1932, on which day he had had a severe chill followed by high fever and a profuse sweat. Three days later a dull aching substernal pain developed, which gradually became worse. This pain seemed to him to be deep in the chest, and it was made definitely worse by deep breathing. He had no more chills after the initial one but continued to have fever. Four days before the onset of his illness he had had a cold in the head, but he had had no cough at any time. There had been a loss of 20 pounds (9.1 Kg) in weight within a month, but he attributed this to hard work. There were no urinary symptoms.

At the age of 19 he had had a bout of fever which lasted for three weeks. He stated that his physician at this time had been unable to determine the cause of the fever. He had contracted gonorrhea at the age of 14, which he stated had been cured. He said that he had never had a primary lesion. Except for an attack of fever which had been diagnosed as malaria, no childhood diseases were recalled. The family history was inconsequential.

*Examination*—Physical examination revealed a well nourished Negro of about the stated age of 24, who did not appear acutely ill. His temperature was 100.8 F, the pulse rate was 96, and the respirations numbered 26 per minute. The tonsils were hypertrophied and appeared moderately inflamed. A few shotty cervical



glands were palpable. The lungs were normal except for the presence of a few coarse moist râles in the base of the right lung, posteriorly. These râles disappeared within a few days. The heart was normal in size and shape, and no murmurs were heard. The blood pressure was 140 mm of mercury systolic and 90 diastolic. The peripheral arteries were soft. The liver and spleen were not palpable.

The urine examined on several occasions always contained pus cells but showed no other abnormalities. The hemoglobin content was 75 per cent, the red blood cells numbered 4,210,000 per cubic millimeter, and the white blood cells, 7,750, with a normal differential count. The complement-fixation and precipitation tests for syphilis were negative. The Widal reaction was positive for *Bacillus typhosus*. The blood and stool cultures for typhoid bacilli were negative.

Roentgenographic study of the chest showed the presence of considerable inflammatory thickening in both lungs without, however, acceptable evidence of tuberculosis.

The remittent type of fever, the temperature never rising above 102 F, gradually became less and disappeared as the body temperature returned to normal on the twelfth day. The symptoms likewise disappeared, and the patient was discharged on April 25 apparently completely recovered. A satisfactory diagnosis was not made, the tentative opinion being that the patient had had mild typhoid fever.

He was readmitted to the hospital on May 11, with distressing shortness of breath and water-logging. He had felt well until May 10, when a severe pain had developed over the upper part of the abdomen, which lasted for only about three days. With the subsidence of the pain, swelling of the abdomen appeared. A few days later he noticed shortness of breath and swelling of the feet. The abdomen continued to increase in size. All symptoms progressively became worse, and for three nights before entering the hospital the patient was forced to sit up in order to breathe and consequently had slept very little.

Physical examination revealed an acutely ill patient. His temperature was 103 F, his pulse rate was 118, and his respirations numbered 30 per minute. Definite cyanosis was present. The veins of the neck, as well as those of the upper extremities, were conspicuously engorged. Many moist rales were present in the bases of both lungs. The area of cardiac dullness was greatly increased both to the right and to the left of the sternum. The heart sounds were distant and indistinct. No murmurs or other adventitious sounds were heard. The pulse was paradoxical in type, at a rate of 118 per minute. The blood pressure was 150 mm of mercury systolic and 90 diastolic. The venous blood pressure was 28 cm of blood. A slight pitting edema over the shins was present. The abdomen was protuberant, and both shifting dullness and a distinct fluid wave were elicited. The liver and spleen could not be palpated owing to the accumulation of fluid.

Examination of the urine showed a trace of albumin, an occasional granular cast and a few leukocytes and erythrocytes. The blood study revealed red blood cells numbering 3,360,000, with a hemoglobin content of 60 per cent, and a white blood cell count of 8,900, with a normal differential count. The blood urea nitrogen was 23.4 mg per hundred cubic centimeters. A blood culture was negative. The renal excretion of phenolsulphonphthalein dye amounted to 50 per cent in two hours. The Wassermann reaction of the blood was negative.

A teleoroentgenogram revealed the presence of a large pericardial effusion.

*Progress*—Pericardial aspiration was done the second day after admission and yielded 300 cc of a slightly blood-tinged fluid. Laboratory examination of this fluid revealed it to be definitely an exudate with a high lymphocyte count. The mechanical removal of the fluid resulted in some improvement. Increasing symp-

toms, however, made it necessary to repeat the pericardial puncture four days later, when removal of 700 cc of a similar fluid relieved the urgent dyspnea. Abdominal paracentesis was attempted on May 19, but without success owing to the fact that the fluid coagulated spontaneously in the trocar. There was a gradual accumulation of fluid in the right side of the chest, which became so great in amount that a thoracentesis was done and 1.5 liters of fluid similar to that obtained from the pericardium was removed. Some time later fluid also appeared in the left pleural cavity.

The temperature remained high for about two weeks and then gradually became lower, returning to normal in about one month. There was no fever for the succeeding two months, and then rises in temperature occurred intermittently, the peaks, which usually occurred in the afternoon, reaching from 101 to 102 F. Inoculation of guinea-pigs with the fluid from both the pleural and the pericardial

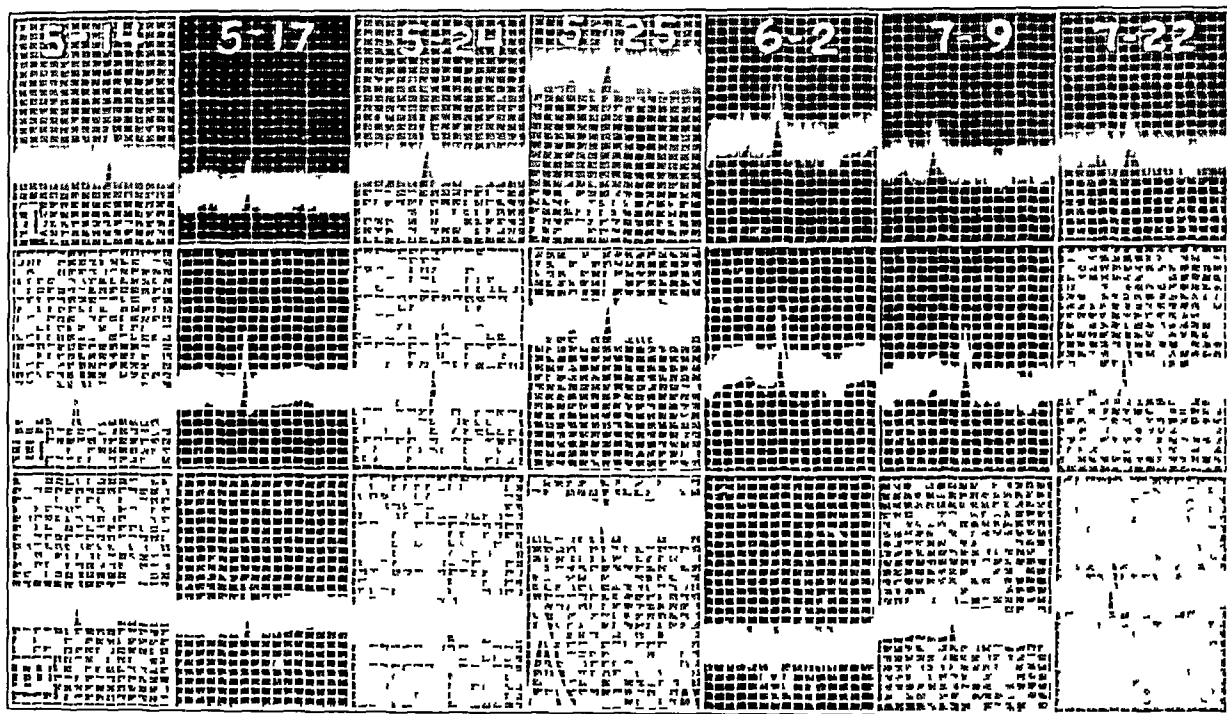


Fig 6 (case 6)—Electrocardiograms in a case of subacute to chronic serous pericarditis, pleuritis and peritonitis. The pericardial effusion was great and persistent.

cavity did not yield any definite evidence as to the etiologic factor. Although inflammatory foci in the lungs, composed of epithelial and lymphocytic cells, suggested tuberculosis, this was not considered definite in view of the fact that no giant cells were found. Stereoscopic roentgenograms of the pulmonary fields demonstrated the absence of any lesion suggesting tuberculosis. In spite of the mechanical removal of the fluid and the dissipation of it by the use of mercurial and xanthine diuretics, the patient's condition was unimproved, and he gradually but progressively became worse. He became dissatisfied and left the hospital against our advice on September 17. Death occurred in a neighboring city approximately five months later.

The clinical diagnosis of multiple serositis or polyserositis was made.

*Electrocardiograms*—Numerous electrocardiographic studies were made. Those depicting the significant changes that occurred are shown in figure 6. The out-

standing findings in the initial curve, taken on May 14, were a QRS complex of less than 5 millivolts in all three leads, associated with marked slurring, a flat  $T_1$ , and low voltage  $T_2$  and  $T_3$ . There were no abnormalities of the RS-T segment. Ten days later, on May 24, early negativity of the T wave was observed in leads I and II, and subsequently, on May 25,  $T_3$  became inverted. Further changes, registered June 2, consisted of an increase in the degree of negativity of the T wave and the appearance of an upward convexity of the RS-T interval. These retrogressed slightly but were still present on July 22. Little, if any, change occurred in the voltage of the ventricular complexes. No Q waves developed.

Electrocardiograms taken before and after paracentesis of the pericardium on two occasions, one before the appearance of the changes in the T wave and one after they had become marked, are shown in figure 7. It is to be noted that little,

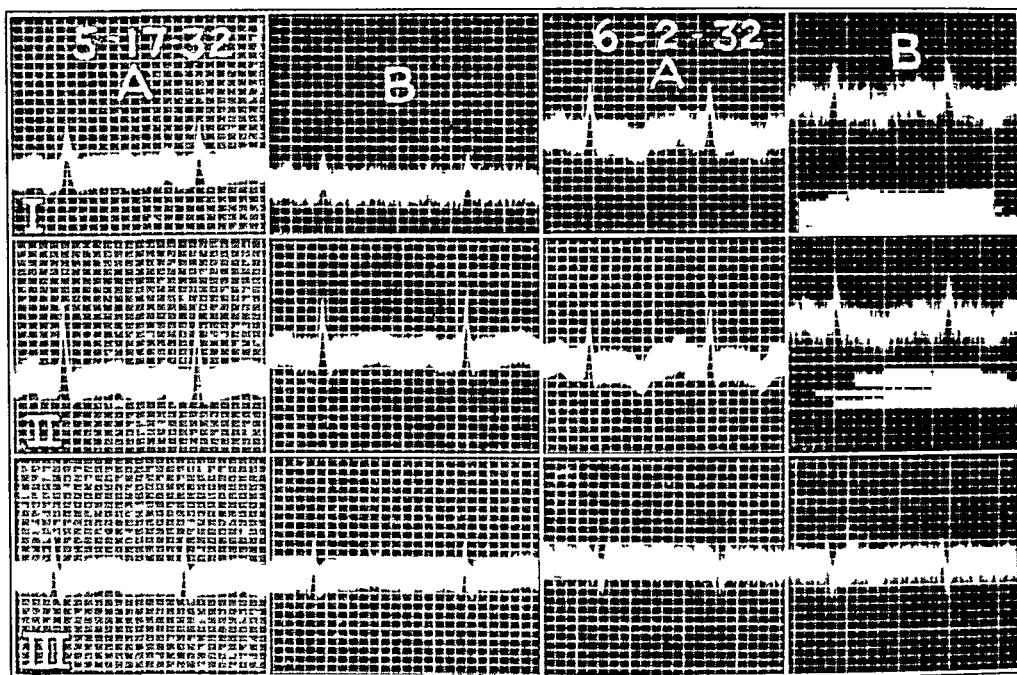


Fig 7 (case 6)—Electrocardiograms taken before (A) and after (B) paracentesis of the pericardium during the early and late stages of the disease. Note the slight change in voltage and that the removal of fluid exerted no effect on the T waves.

if any, change in the T waves occurred. In the first instance 700 cc of fluid was aspirated and in the second, 500 cc. In each instance there was a slight decrease in the voltage of the ventricular complexes after the removal of the fluid.

**CASE 7—History**—E. W., a Negro laborer, aged 38, was admitted to the John Sealy Hospital at 2:30 a. m. on May 31, 1930. At 7:30 a. m. the previous day, in a nearby city, he had been shot with a shotgun from a considerable distance and had sustained numerous bird-shot wounds, two of which were in the anterior wall of the chest overlying the heart. He was seen by a physician at that time, who did not regard his injuries as being serious and who administered tetanus antitoxin. Shortly thereafter, however, shortness of breath and pain in the epigastrium and precordium appeared, all of which symptoms gradually increased in intensity.

*Examination*—Physical examination revealed a Negro of about the stated age of 38, who appeared to be critically ill. Dyspnea was extreme, and definite cyanosis was present. The cervical veins were greatly distended. The pulse was very rapid and barely perceptible at the wrist. The blood pressure could not be recorded. A small puncture wound was present in the fourth left intercostal space about 2 cm from the left sternal border, and another in the fifth left intercostal space about 4 cm from the sternum. A marked increase in the area of cardiac dullness was noted on percussion. On auscultation, the heart sounds were feeble, indistinct and distant. Considerable tenderness was present in the upper part of the abdomen. The liver and spleen could not be felt.

A teleroentgenogram revealed the presence of a large amount of fluid in the pericardium.

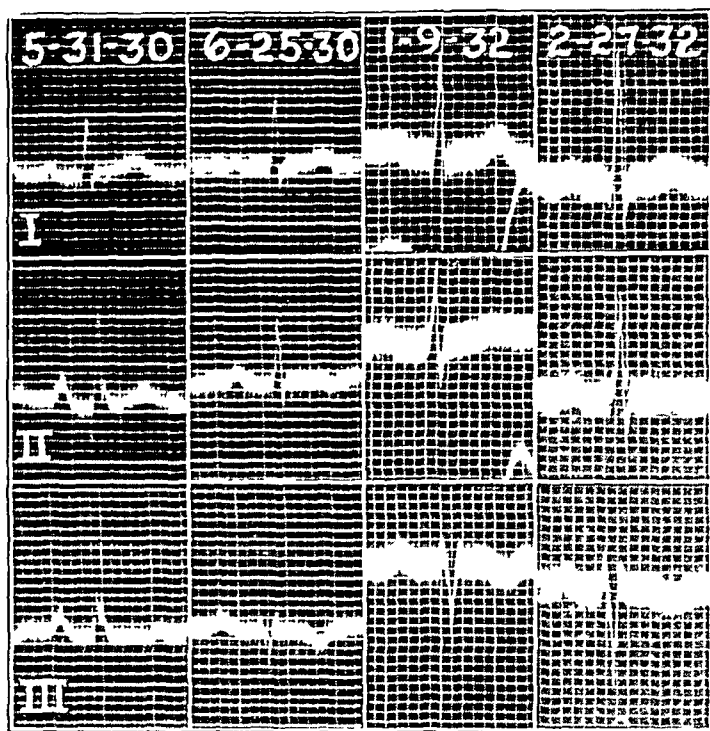


Fig 8 (case 7) —Electrocardiograms in a case of hemopericardium following a gunshot wound. Severe heart tamponade was present and necessitated paracentesis. Recovery was complete.

In view of the urgency of the symptoms, paracentesis of the pericardium was done, and 250 cc of blood was removed. The change in the patient's condition was dramatic. The blood pressure rose to 100 mm of mercury systolic, the pain and dyspnea were much relieved and the patient appeared greatly improved. Four days later, on June 4, a teleroentgenogram showed that considerable fluid remained in the pericardium. Nevertheless, his condition remained good, and at the end of two weeks the patient seemed to have made a complete recovery. An additional roentgenographic study was made on June 23, and at that time the cardiac shadow was of normal size and configuration. Two bird-shots were noted on the film, one was embedded in the wall of the chest, and the other, by fluoroscopy, was found to be embedded in the wall of the right ventricle.

*Electrocardiograms*—The initial electrocardiogram taken on May 3, 1930, before aspiration of the pericardium was rather noncommittal from a diagnostic standpoint.

(fig 8) A slight positive deviation of the RS-T sector was present in leads I and II.  $T_1$  and  $T_2$  were upright and of fair voltage and  $T_3$  was inverted. The P wave in derivations II and III was sharply peaked and of good amplitude. The second electrocardiogram, recorded on June 25, showed definite inversion of the T wave with an upwardly convex RS-T sector in leads II and III. A shift in the electrical axis had occurred. In addition, there was a rather striking change in the configuration and amplitude of the P wave. Subsequent curves were taken on Jan 9 and Feb 27, 1932. The T wave in lead II had become upright but was of low voltage, and  $T_3$  remained sharply inverted. There was a progression of the shift of the electrical axis. Curves taken in three positions on February 27 showed some fixation of the electrical axis. No Q waves were apparent.

#### COMMENT

Our clinical observations and experimental studies,<sup>8</sup> with those of others,<sup>12</sup> seem to furnish conclusive proof that pathologic states of the pericardium are capable of producing definite and striking alterations in the electrocardiogram. Broadly speaking, these changes may be of three types: a decrease in the voltage of the QRS complex, deviations of the RS-T sector from the iso-electric level, and the progressive changes in the T wave, the development and interpretation of which we are emphasizing as our contribution to the subject. The deviations of the RS-T sector and the decreased voltage usually occur early and in the presence of rapidly accumulating effusion of blood in the pericardium. The changes in the T wave come later and may or may not have been preceded by deviations of the RS-T sector. The abnormalities of the RS-T sector are not present in all cases of pericardial effusion, even in those instances in which the accumulation of fluid is great. In case 6, the amount of fluid present was sufficient to produce *Hemistamponade* with extreme venous congestion, a decrease in systemic blood pressure and diastolic heart failure, yet the RS-T segment remained at the iso-electric level. A moderate degree of effusion was present in cases 3 and 5, and no changes in the RS-T interval were recorded. Extensive pericardial effusion, likewise, may not be accompanied by significant decrease in the voltage of the QRS complex of the electrocardiogram. In case 6 the initial deflection of the ventricular complex was less than 5 millivolts in all three leads. It is interesting to note that in this case, on two occasions, an electrocardiogram taken immediately following paracentesis with the removal of 700 and 600 cc of fluid, respectively, showed an actual and unexplained decrease in the amplitude of the QRS complex (fig 7). In case 2, one of acute fibrinous pericarditis without effusion, the QRS complex was less than

<sup>12</sup> Katz, L. N., Feil, H. S. and Scott, R. W. The Electrocardiogram in Pericardial Effusion, Experimental, *Am Heart J* **5** 77 (Oct.) 1929. Foulger, M., and Foulger, J. H. The Blood Pressure and Electrocardiogram in Experimental Pericardial Effusion, *Am Heart J* **7** 744 (Aug.) 1932.

5 millivolts in all leads, and this finding persisted without change throughout the course of the disease and after complete recovery. The amount of fluid present, the nature of the fluid substance, the rapidity of accumulation, the distensibility of the pericardial sac and the presence or absence of coronary sclerosis are factors which appear to determine whether or not these electrocardiographic signs will appear.

In the cases of pericarditis associated with an effusion that have been studied adequately by serial electrocardiograms, the disappearance of the changes in the RS-T segment was followed by definite alterations in the T wave. Similarly, in the cases of fibrinous pericarditis without appreciable exudation into the pericardial sac, successive changes in the T wave which were not preceded by deviations in the RS-T sector have been recorded. The alterations in the T wave are essentially identical in the two types of cases and consist, as a rule, of an upward convexity of the RS-T interval, which is followed by a sharply peaked, inverted T wave. In occasional cases in the literature no convexity of the RS-T sector or negativity of the T wave was present, there were merely iso-electric intervals and flattened T waves. These abnormalities of the end-deflection of the ventricular complex appear early and by the end of the first week or ten days are quite definite. As the condition progresses, the negativity of the T wave frequently becomes more marked and successively becomes apparent in all three leads, the initial change being, as a rule, in lead I. Subsequently, with the passage of the acute stage, the changes in the T wave gradually disappear, usually in the same order as they developed. In those cases in which recovery is apparently complete, the T wave again becomes upright in the significant leads. A careful study of the electrocardiograms here presented indicates that the changes in the final deflections of the ventricular complex are similar in many, but not in all, respects to those encountered in the healing stages of cardiac infarction.

#### AN EVALUATION OF THE ELECTROCARDIOGRAPHIC DIFFERENTIATION BETWEEN PERICARDIAL DISEASE AND CARDIAC INFARCTION

Acute pericardial disease, particularly when associated with pain, may simulate closely the syndrome of coronary thrombosis with infarction, and in view of the fact that pericarditis is a frequent finding in the latter condition the difficulty in differential diagnosis is obvious. When there are added to these clinical similarities almost identical electrocardiographic abnormalities, the diagnostic problem becomes still further involved. The importance of an exact diagnosis from a therapeutic as well as from a prognostic standpoint is self-evident. In lieu of pathognomonic electrocardiographic findings, our analysis of all available data offers some highly suggestive electrocardiographic signs,

which only careful scrutiny of serially taken curves will reveal and which when found should materially aid in arriving at an accurate diagnosis

With reference to the abnormalities of the RS-T segment, it is to be noted that in pericardial effusion the elevation may occur in all three leads, or in leads I and II, there being no cases reported in which the RS-T sectors of lead II and lead III alone were abnormal. Furthermore, as Scott, Katz and Feil<sup>1</sup> pointed out, these deviations in the RS-T interval are always positive. The paradoxical relationship between leads I and III is not present in uncomplicated pericarditis. Exceptions to the latter rule are the cases of pericardial effusion reported by Gager<sup>6</sup> and Cohn and Swift<sup>5</sup>. In the former instance, the patient's age, the presence of hypertension and peripheral and fundal sclerosis and the sudden onset strongly suggest that a coronary thrombosis inaugurated the breathlessness and effusion. The Q waves in the initial curve and the subsequent electrocardiographic studies further support this contention. In Cohn and Swift's case the findings are somewhat obviated due to the fact that digitalis had been administered. Some of our observations, especially in the experimental animal, suggest that after deviations of the RS-T segment the return to the iso-electric level occurs sooner in pericardial effusion than in cardiac infarction, especially is this so when the increased intrapericardial pressure is relieved.

In the matter of abnormalities of the T wave, from the standpoint of configuration no differentiating evidence is forthcoming. The so-called "coronary" type of T wave is commonly encountered in cases of pericardial involvement. Inversion of the T wave in leads I and II in cases of pericarditis is seen, as a rule, during some stages of the disease, and negativity of the T wave is frequently present in all three leads. In contrast to the changes in the RS-T sector in cases of pericarditis, a paradoxical relationship of the T waves in leads I and III may be present in the early stages produced by a negative  $T_1$  and a positive  $T_3$  and in the later stages by a persistence of negativity of the T wave in lead III with a return of  $T_1$  to positivity.

A further important point in differential diagnosis from an electrocardiographic standpoint seems to be found in a study of the initial deflections of the ventricular complex. As Wilson and his co-workers<sup>13</sup> have so ably pointed out, the changes in the Q wave following closure of the coronary artery with infarction are quite distinctive and frequently diagnostic. These changes occur in a high percentage of cases and usually appear following the disappearance of the abnormalities of the

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13 Wilson, F. N., Macleod, A. Garrard, Barker, Paul S., Johnston, Franklin D., and Klostermeyer, L. L. The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex. *Heart* 16 155 (June) 1933.

RS-T segment They are associated with the alterations of the T wave and frequently persist after the disappearance of the latter changes In an analysis of the reported cases of pericarditis studied electrocardiographically, including those of this series, conspicuously abnormal changes in the Q wave were not observed except in those of Gager<sup>6</sup> and Agostoni and Papp<sup>9</sup> As previously mentioned, Gager's case appears to be one of definite coronary artery disease The electrocardiograms of the case of Agostoni and Papp revealed both auriculo-ventricular and bundle branch conduction defects and hence cannot be considered in this connection In case 4 of this series, it is to be noted that an inconspicuous Q wave was present in all three leads However, the Q waves are similar in size and configuration to those encountered normally and, furthermore, throughout the two year period of study they showed no appreciable change It seems logical, therefore, to consider the presence of definite abnormalities of the Q wave as evidence in favor of the diagnosis of myocardial infarction rather than that of an uncomplicated pericarditis

An anteroposterior chest lead, lead IV, was taken according to the technic of Wolferth and Wood,<sup>14</sup> in two of the cases herein reported A review of the reported cases of acute obstruction of the coronary artery studied with the use of this additional lead reveals that when changes in the RS-T interval are present in the conventional leads they are likewise present in lead IV, frequently being more marked, and, furthermore, that deviations in the RS-T interval may be present in lead IV without being apparent in the conventional leads Although the number of cases of pericarditis studied with the fourth lead is far too small to justify any conclusions, the findings hitherto reported as pathognomonic of occlusion and disease of the coronary artery have been noted In case 4, definite deviations in the RS-T segment (slightly more than 1 millivolt) were present in the three conventional leads along with a similar but less marked change in the chest lead Subsequently, with the development of changes in the T wave in the usual leads, further significant changes in lead IV appeared, consisting of a negative, humped RS-T segment with a positive coronary T wave In the second instance of pericardial effusion (case 3), also studied with the fourth lead, no changes in the RS-T interval were present in the conventional leads It is interesting to note, however, that in lead IV, before the appearance of changes in the T wave in the conventional leads, a type of change had occurred which has been considered suggestive of coronary artery disease

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14 Wolferth, C. C., and Wood, F. C. The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am J M Sc* **183** 30 (Jan) 1932



THEORETICAL CONSIDERATIONS AS TO THE MECHANISMS UNDERLYING  
THE PRODUCTION OF THE ELECTROCARDIOGRAPHIC  
CHANGES IN PERICARDITIS

Our interpretation of the results of our clinical and experimental studies and those of others seem to indicate the presence of two distinct types of electrocardiographic changes occurring in different stages of pericardial processes. The one appearing during the acute stage often consists of elevation of the RS-T sector and decreased voltage of the ventricular complex, and the other, occurring later, is comprised of progressive and retrogressive changes in the T wave.

The deviations in the RS-T sector are apparently the result of ischemia of the cardiac muscle, occurring as the intrapericardial pressure rises to the point of collapsing the auricles, thereby hindering venous return, lowering the systemic pressure and pulse pressure and thus interfering materially with the blood flow through the right and left coronary arteries. This total involvement of the coronary flow is probably what accounts for the positive deviation of the RS-T sector in all leads.

The decreased voltage of the QRS complex seen in cases of pericardial effusion has been attributed to the change in the conducting medium surrounding the heart with a consequent short-circuiting or damping of the action currents. In view of the fact that numerous cases fail to show this electrocardiographic sign, it becomes necessary to consider other possibilities. Myocardial edema, pulmonary engorgement, pleural effusion and subcutaneous edema are other factors which might be operative in the production of this electrocardiographic abnormality.

As the changes in the T wave occur in cases of acute fibrinous pericarditis without effusion and, further, in view of the fact that these abnormalities also appear after the effusion has become reabsorbed and, in our animals during healing, it seems likely that they are associated with organization and repair of the process in the epicardium and subepicardial myocardium. These changes occur regardless of the etiologic factor at work in the pericardial process. In other words, whether the organization is of tissue of rheumatic, tuberculous, pyogenic or nonspecific etiology, or even when it is the organization of blood that is deposited on the epicardium the changes in the T wave are qualitatively the same. The length of time for which the abnormalities of the T wave persist, however, varies somewhat with the etiologic factor. In the tuberculous type, with a tendency to recurrent flare-ups, they may continue indefinitely, while in rheumatic pericarditis they usually clear up within a few weeks after subsidence of the symptoms. Apparently, with each recurrence the changes are more likely to persist, and the length of time they remain apparent may be considered as

somewhat of an index to the degree and extent of involvement. In cases of hemopericardium, in which drainage is done by paracentesis and in which there is no recurrence, the T waves return to normal much sooner than in cases in which the blood is allowed to remain in the pericardium.

#### SUMMARY

Seven cases of pericardial disease of various types are presented with abstracts of the clinical histories, complete physical and pertinent laboratory data and serial electrocardiographic studies.

A complete review of the available literature on the subject has been attempted.

The similarity of the deviations in the RS-T sector in cases of pericardial effusion to those occurring in cases of coronary thrombosis with infarction is reiterated.

Attention is directed to the previously unmentioned but significant inversions of the T wave which follow the changes in the RS-T segment in cases of excess fluid in the pericardial sac following reabsorption, thus continuing the electrocardiographic analogy between pericardial effusion and cardiac infarction.

The occurrence of progressive changes in the T wave in acute fibrinous pericarditis without an accompanying effusion and without preceding abnormalities in the RS-T segment is emphasized.

An evaluation of the electrocardiographic differences between pericardial disease and cardiac infarction is presented. The absence of the development of significant abnormalities of the Q wave in pericardial pathologic processes is stressed. No information of differential diagnostic value is apparently to be derived from the use of lead IV.

Some theories as to the mechanisms operative in the production of the types of electrocardiographic changes encountered, based on our clinical and experimental studies, are brought forth. The changes in the RS-T sector are apparently the result of ischemia of the cardiac muscle, and the progressive and retrogressive changes in the T wave seem to be associated with organization and repair of the process in the epicardium and subepicardial myocardium.

# EXPERIMENTAL PERIPHERAL GANGRENE

## EFFECT OF ESTROGENIC SUBSTANCE AND ITS RELATION TO THROMBO-ANGIITIS OBLITERANS

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The present studies have their genesis in an effort to open a new avenue of approach to the problem of thrombo-angitis obliterans. Perusal of the literature adequately demonstrates the confusion surrounding the clinical and experimental aspects of this disturbance. What knowledge one has concerning the malady has been gleaned from purely clinical and statistical research. Experimental investigation,<sup>1</sup> directed almost exclusively toward establishing a specific bacterial etiologic agent for the disease, has thus far either failed completely or the results have been so meager as to be altogether inconclusive.

It would appear rather facetious to state that in an endeavor to reproduce experimentally a pathologic entity one must first know the pathology. Nevertheless it is here that the first difficulty is encountered. There is no unanimity of opinion among students of the disease regarding the pathology of thrombo-angitis obliterans. Buerger,<sup>2</sup> in his descriptions of the pathogenicity and chronologic pathology, postulated the following series of events. There is an initial acute inflammation with polymorphonuclear leukocytic invasion of the perivascular tissues and of all the coats of the vessel. Synchronously, thrombosis occurs in the area of inflammation. This is followed by replacement of the inflammatory cells by connective tissue, organization and canalization of the thrombus and finally a great overgrowth of connective tissue in and about the adventitia binding the artery, the vein and the nerve.

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1 (a) Rabinowitz, H M. Experiments on the Infectious Origin of Thrombo-Angitis Obliterans and the Isolation of a Specific Organism from the Blood Stream, *Surg, Gynec & Obst* **37** 353, 1923. (b) Buerger, Leo. Thrombo-Angitis Obliterans. Experimental Reproduction of Lesions, *Arch Path* **7** 381 (March) 1929. (c) Horton, B T, and Dorsey, A H E. Experimental Thrombo-Angitis Obliterans. Bacteriologic and Pathologic Studies, *Arch Path* **13** 910 (June) 1932.

2 Buerger, Leo. Thrombo-Angitis Obliterans. A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, *Am J M Sc* **136** 567, 1908. Is Thrombo-Angitis Obliterans an Infectious Disease? *Surg, Gynec & Obst* **19** 582, 1914, *The Circulatory Disturbances of the Extremities*, Philadelphia, W B Saunders Company, 1924.

together. Mahorner,<sup>3</sup> Telford and Stopford<sup>4</sup> and others have expressed the opinion that the earliest pathologic process consists in the invasion of the adventitia by lymphocytes. This change is associated with cellular proliferation of the intima. Subsequently a thrombus forms, completing the occlusion of the vessel. The thrombus becomes organized and canalized, with replacement of the inflammatory cells by connective tissue. This lesion progresses to a fibrous matting together of the artery, vein and nerve. These authors specifically stated that the disease is essentially chronic rather than acute and that intimal proliferation probably precedes the deposition of the thrombus rather than occurring simultaneously with it. Another disputed point is the presence or absence of an increase of elastic tissue in the intima. Still another is the significance of giant cells in the lesion. Bueiger spoke of them as characteristic. Other investigators made little mention of them. With regard to the media of the affected vessels, Mahorner noted that the muscle cells are well preserved and rarely show a change except late in the disease, when they may be atrophied and show some increase in interstitial connective tissue. Telford and Stopford remarked that the amount of muscular tissue in the media is much reduced and that the fibers are separated by fibrous connective tissue. Mahorner observed that the internal elastic membrane is not split. Telford and Stopford observed that it was fragmented and fibrillated. So unsettled is the question that Horton and Dorsey<sup>1c</sup> expressed doubt as to whether the lesion of thrombo-angitis obliterans is a distinct entity and remarked that until this is settled the results of experiments on animals must not be held to be conclusive.

Previous experimenters, in attempts to disclose a specific etiologic agent, took as their pathologic criteria intimal proliferation and thrombus formation, together with gross trophic disturbances in the area distal to and supplied by the occluded vessel.<sup>5</sup> This is true of the work of Rabinowitz<sup>1a</sup> and Horton and Dorsey<sup>1c</sup> and of the observations of Kaunitz<sup>6a</sup> with ergot. These are the two points on which most patholo-

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3 Mahorner, H. R., in Brown, G. E., Allen, E. V., and Mahorner, H. R. *Thrombo-Angitis Obliterans*, Mayo Clinic Monograph, Philadelphia, W. B. Saunders Company, 1928.

4 Telford, E. D., and Stopford, J. S. B. *Thrombo-Angitis Obliterans*, Brit. M. J. **2** 1035, 1924.

5 This is not entirely true of the recent work of Schmidt-Weyland (*Klin. Wchnschr.* **11** 2148, 1932). While these were the major observations, leukocytic infiltration was also evident. His method was somewhat of a departure from the customary methods of experimentation in this field.

6 (a) Kaunitz, J. *The Pathologic Similarity of Thrombo-Angitis Obliterans and Endemic Ergotism*, *Am. J. Path.* **6** 299, 1930, (b) *Chronic Endemic Ergotism. Its Relation to the Vasomotor and Trophic Diseases*, *Arch. Int. Med.* **47** 548 (April) 1931, (c) *Chronic Endemic Ergotism. Its Relation to Thrombo-Angitis Obliterans*, *Arch. Surg.* **25** 1135 (Dec.) 1932.

gists seem to agree, although, as has already been indicated, the sequence of even these two phenomena is still debated

This review indicates that the actual reproduction of a lesion the pathologic process of which has not been definitely determined is scarcely feasible. On the other hand, if one can produce a lesion comparable to that pathologic process which affects the same system—the vascular tree—and shows on histologic examination changes similar to those in the disease under investigation, one is, I believe, justified in pointing out corollaries in terms of the disease in question. However, it is further necessary that the pathologic process be produced regularly in the experimental animals. As I have previously indicated, attempts to establish such a lesion with bacterial agents have been, at best, suggestive rather than conclusive. Certainly they have not met with a regularity of success which would render any experimental manipulation amenable to a mathematical analysis of the results.

In recent years Kaunitz<sup>6</sup> has emphasized the rather striking similarity, both clinical and pathologic, between ergotism and thrombo-angitis obliterans. His development of this theorem is adequately presented and at this time needs no further elaboration. He found that both in acute and in chronic ergot intoxication gangrene was produced. Histologic examination demonstrated definite intimal proliferation, thrombus formation, organization of the thrombus and recanalization. These are all the criteria customarily required by investigators in this field. Whether or not there is such an etiologic relationship between ergot and thrombo-angitis obliterans as Kaunitz suggested is difficult to say. Certainly I am not desirous of recording myself as subscribing to this theory. Nevertheless, I feel that one may reasonably accept ergot arteritis and ergot gangrene as a typical pathologic process on which to base further studies. The results, while not directly translatable in terms of thrombo-angitis obliterans, at least suggest possibilities in the ultimate solution of the problem.

Two factors in the procedure of Kaunitz, however, were unsatisfactory for my purposes. He used the cock, the comb of which is not so analogous to the arterial tree in man as is desirable. Moreover, ergot was employed in the form of the whole drug which is not amenable to careful dosage and contains at least four vasotropic substances: histamine, tyramine, choline and its derivatives and the specific alkaloid of the fungus. Fortunately, in 1923, Rothlin,<sup>7</sup> working with ergotamine, the alkaloid isolated from ergot by Stoll in 1918, found that it possessed not only the same physiologic but also the same toxicologic

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7 Rothlin, E. Recherches experimentales sur l'ergotamine, alcaloïde spécifique de l'ergot de Seigle, Arch. internat. de pharmacodyn. et de therap. **27** 459, 1923.

action as does the whole fungus. He found that albino rats given toxic quantities of ergotamine tartrate showed within from five to seven days thereafter pallor of the end of the tail, followed by marked congestion, the tail becoming blue, then black, finally demarcation occurred, and the distal gangrenous portion dropped off, the proximal stump healing over. Polak,<sup>8</sup> in 1924, experimenting with the gangrene of ergotamine intoxication, found that section of the abdominal sympathetic chains definitely hastened the onset of the gangrene, while the administration of epinephrine markedly delayed the process. Both these investigators found that gangrene of the rat's tail was produced regularly by ergotamine. It is this method—the administration of toxic quantities of ergotamine to white rats—which I adopted for the present studies.



Fig 1—Rat's tail sixteen days after an injection of ergotamine

The experiments of Rothlin<sup>7</sup> were repeated, and the gross phenomena described by him were duplicated. Male and female albino rats weighing from 140 to 170 Gm were given an intoxicating dose of ergotamine tartrate (gynergen)<sup>9</sup>. The drug was administered subcutaneously, the dose varying in successive groups from 25 to 100 mg per kilogram of body weight. It was found that in the females as well as in the males even the lower limit of these dosages was sufficient to produce gangrene of the tail. Unlike the experience of Rothlin,<sup>7</sup> the pregangrenous changes in my animals did not always occur within from five to seven days. With greater doses of ergotamine pallor of the tail appeared as early as the third day, while cyanosis and gangrene were

8 Polak, E. Experiments on Ergotism, *Časop lek cesk* **63** 1409, 1924

9 The gynergen, sandoz, and theelin, Parke, Davis and Co., used in these studies were the standard products, purchased in the open market

sometimes delayed as late as from the twenty-eighth to the thirty-third day. When demarcation became definite (fig. 1), the animal was anesthetized with ether and the entire tail amputated between ligatures. Sections were taken at various levels.

#### PATHOLOGY OF ACUTE ERGOTISM

As Rothlin<sup>7</sup> clearly described, the symptoms manifested by the rats immediately following the injection of ergotamine were those of acute intoxication, lasting for about two hours, at the end of which time the animals recovered spontaneously and were to all appearances normal. On from the third to the fifth day (table 1), in proportion to the dose of ergotamine, the end of the tail became pale for a variable distance and was distinctly more sensitive to touch than was the

TABLE 1—*Mean Day of Onset of the Trophic Changes and Extent of the Gangrene in the Tails of the Four Series\**

	Pallor	Cyanosis	Blackening	Demarcation	Extent of Gangrene, Inches
Series 1	4.90 ±0.117520	9.36 ±0.151600	16.16 ±0.434025	20.00 ±0.464860	1.72 ±0.065533
Series 2	4.45 ±0.111597	8.25 ±0.125054	12.50 ±0.228731	16.20 ±0.309458	1.92 ±0.087205
Series 3	3.95 ±0.075032	7.80 ±0.107707	10.80 ±0.151445	14.55 ±0.226105	1.96 ±0.083804
Series 4†	3.00 ±0.00	6.38 ±0.342524	9.83 ±0.473983	16.16 ±1.932614	1.91 ±0.107088

\* The figures in the first four columns represent the mean day of onset of the indicated trophic disturbance in rats receiving ergotamine only. The figures in the fifth column represent the mean length of the tail involved in the gangrenous process in inches.

† The extent of the gangrene developing in the two rats of series 4 (see text) which received theelin was  $\frac{3}{8}$  and  $\frac{1}{2}$  inch, respectively.

proximal portion. The pallor gradually faded and by the sixth to the ninth day was replaced by marked cyanosis. The rat could still move the tail throughout its entire length and apparently suffered exquisite pain when the affected area was touched. The involved portion soon became black, dry, hard and anesthetic. It was demarcated on from the sixteenth to the twentieth day, and thereafter the distal gangrenous portion sloughed off, leaving a proximal stump, which healed. About the time that cyanosis was pronounced in the tail an area of local necrosis appeared on the back of the animal at the point of injection of the ergotamine. This separated and was ultimately cast off and replaced with new skin.

The predominant histopathologic feature was the marked cellular proliferation and swelling of the intima. This was most evident in the smaller arteries and arterioles, where in some sections the lumens

were almost completely occluded (fig 2). To some extent the process involved the veins and, to a lesser degree, the large central artery of the tail. In the latter vessel the outstanding pathologic change was the presence of a thrombus (fig 3). The intima had become adherent to the occluding mass and in places had been drawn completely away from the internal elastic membrane. At other points there seemed to

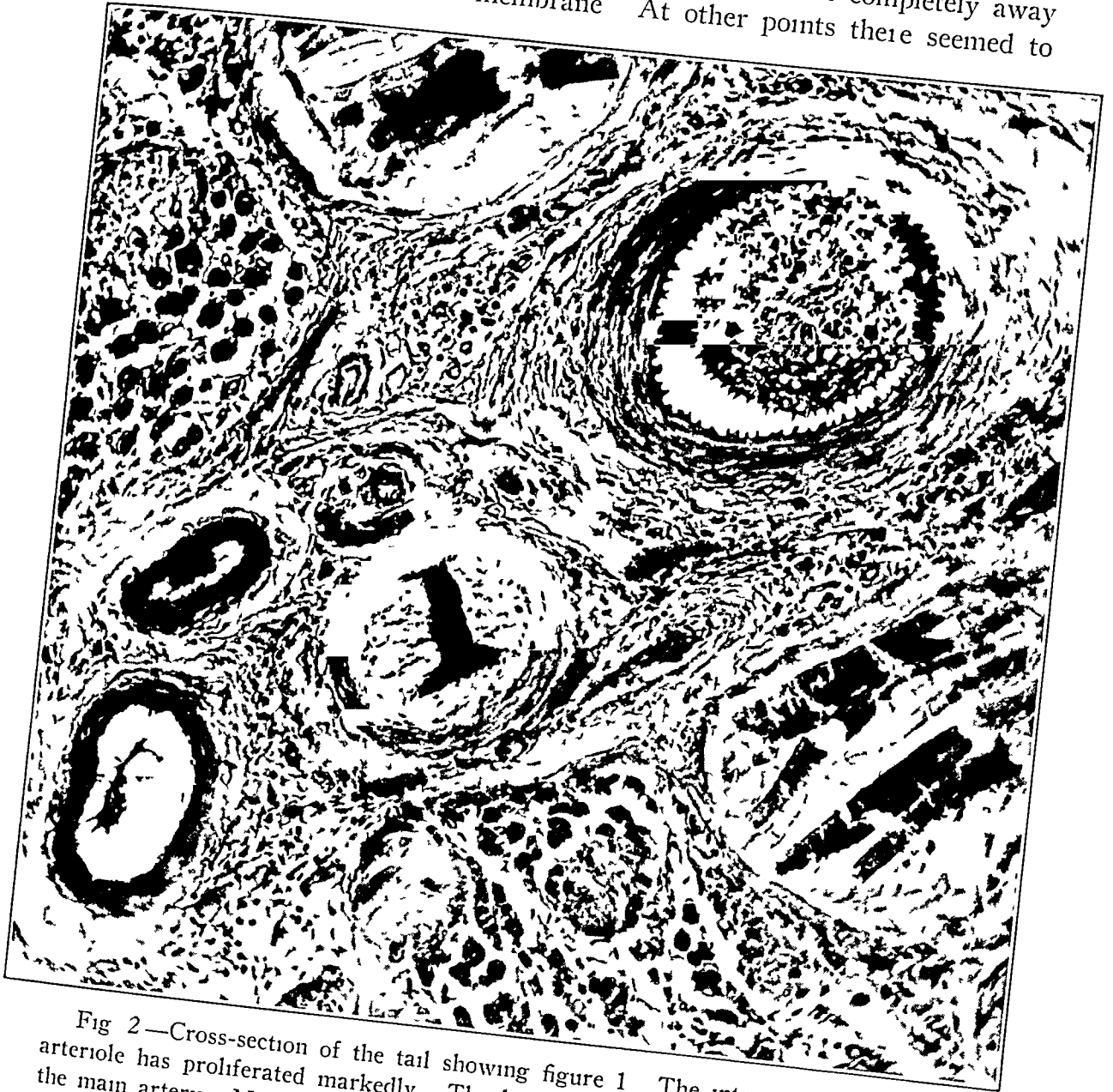


Fig 2—Cross-section of the tail showing figure 1. The intima of the central arteriole has proliferated markedly. The large vessel containing the thrombus is the main artery. Magnification,  $\times 200$ .

be a definite attachment to the wall of the vessel. In sections taken from tails in which demarcation was complete the thrombus had rapidly become organized and canalized (fig 4), the penetrating channels demonstrating in high power magnification a definite endothelial lining. The internal elastic membrane was intact throughout, and while the muscle cells of the media were usually edematous the



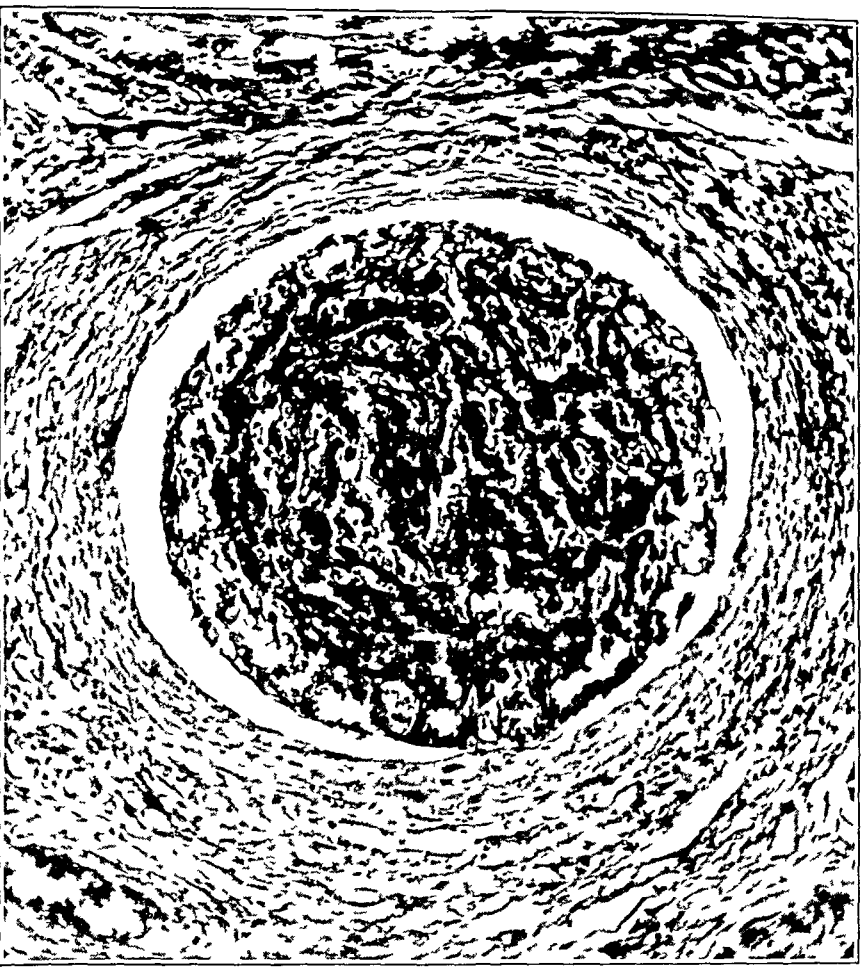


Fig 3—Cross-section of the tail, showing the thrombus occluding the central artery Magnification,  $\times 200$

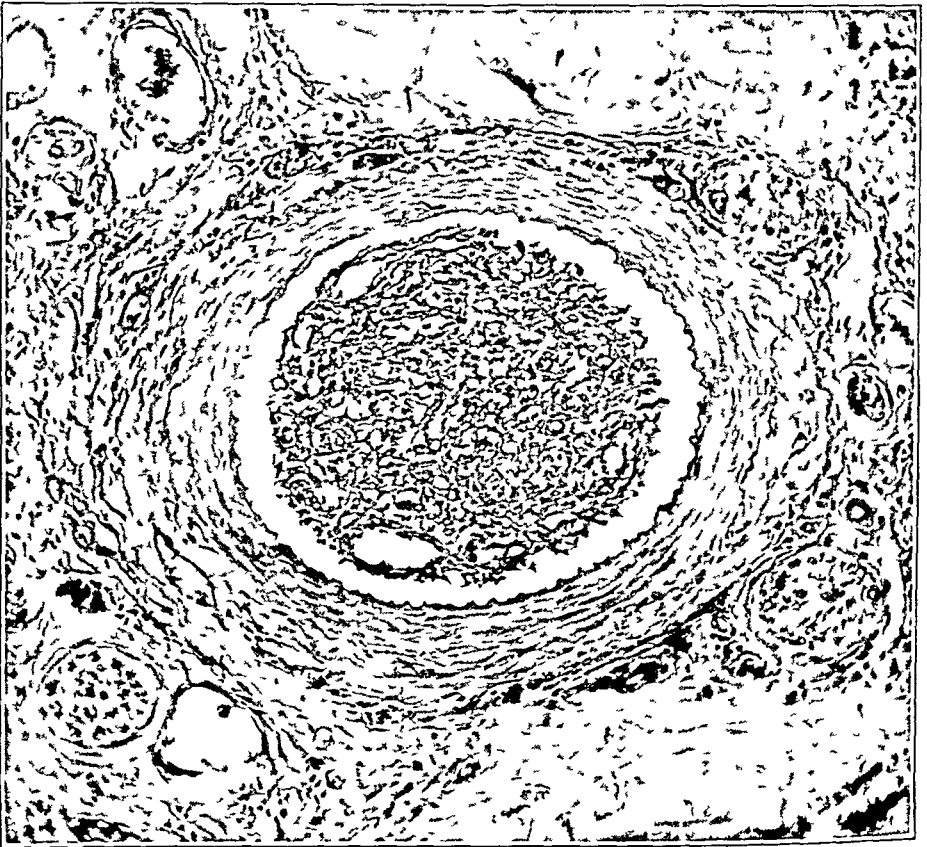


Fig 4—Cross-section of the tail, showing the occluding thrombus to have undergone canalization Magnification,  $\times 200$

characteristic changes present were confined within this barrier. There was no appreciable leukocytic reaction either within the coats of the arteries or arterioles or in the periarterial tissues.

The veins, on the other hand, especially those superficially located, while demonstrating intimal proliferation and thrombosis, in many sections showed in addition marked thrombophlebitis (fig 5). In those areas the perivenous tissues, as well as the adventitia and the media of the vein and the thrombus were invaded by polymorphonuclear



Fig 5—Cross-section of the tail, showing the area of thrombophlebitis. The thrombus, the walls of the vessel and the perivenous tissues are invaded by polymorphonuclear leukocytes. Magnification,  $\times 200$ .

leukocytes. The only noticeable change in the nerves was that in high power magnification there appeared to be vacuolation of the myelin sheaths. Such inflammatory reaction as was present, other than that in the phlebotic areas, was restricted to the zone of demarcation. Here I observed masses of leukocytes, both neutrophilic and lymphocytic, while advancing distally into the inflammatory area were sheets of young fibroblasts. It seems more logical to interpret this reaction as a part of the process of healing than to consider it a response to the irritant.

It is to be emphasized that the changes described occurred in the tail, remote from the site of injection of ergotamine, which in all the animals was on the back, high up toward the shoulders. It is further to be noted that I was dealing with the manifestations of an acute rather than a chronic lesion. Experiments consisting in the protracted feeding of ergot to rats in order to study the lesions of chronic ergotism in these animals are in progress at the present time. For the moment, however, since the purpose was to approach the problem of thrombo-angitis obliterans from an etiologic angle, I was particularly desirous of approximating the earlier lesions of the disease. With this in mind, two things were important. First, the lesions were produced regularly both in male and in female rats. Second, the microscopic lesions consisted in cellular proliferation of the intima, thrombus formation, organization and recanalization of the thrombus, thrombophlebitis and ischemic or toxic changes in the nerves. These, I believe, warrant the premise that while I have not and do not claim to have reproduced thrombo-angitis obliterans, nevertheless I produced a pathologic condition which grossly and microscopically is sufficiently analogous to this disease to justify further experimental study.

#### EXPERIMENTAL STUDIES

Having definitely established the regularity of the production of gangrene in the rat's tail by the use of ergotamine, I proceeded to the immediate problem. Among what appear now to be firmly established facts in the etiology of thrombo-angitis obliterans, two are outstanding. The first is the deleterious effect of tobacco smoking on the progress of the disease. While the etiologic position of tobacco in thrombo-angitis obliterans is still a moot point, clinically tobacco is universally indicted,<sup>10</sup> and the clinical-experimental studies of Barker,<sup>11</sup> Maddock and Coller,<sup>12</sup> Harkev<sup>13</sup> and Sulzberger and his associates<sup>14</sup> seem defi-

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10 Meyer, W. Etiology of Thrombo-Angitis Obliterans, *J A M A* **71** 1268 (Oct 19) 1918, A Further Contribution to the Etiology of Thrombo-Angitis Obliterans, *M Rec* **97** 425, 1920. Silbert, S. Studies on Thrombo-Angitis Obliterans (Buerger). II The Effectiveness of Therapeutic Procedures, *J A M A* **89** 964 (Sept 17) 1927. Samuels, S. S. Gangrene Due to Thrombo-Angitis Obliterans. Further Experiences with Treatment, *J A M A* **102** 436 (Feb 10) 1934.

11 Barker, N. W. The Tobacco Factor in Thrombo-Angitis Obliterans, *Proc Staff Meet, Mayo Clin* **6** 65, 1931, Vasoconstrictor Effects of Tobacco Smoking, *Proc Staff Meet, Mayo Clin* **8** 284, 1933.

12 Maddock, W. G., and Coller, F. A. Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angitis Obliterans, *Ann Surg* **97** 70, 1933.

13 Harkev<sup>y</sup>, J., Hebal<sup>d</sup>, S., and Silbert, S. Tobacco Sensitiveness in Thrombo-Angitis Obliterans, *Proc Soc Exper Biol & Med* **30** 104, 1932.

14 Sulzberger, M. B., Scholder, B., and Feit, E. Studies in Tobacco Hypersensitivity, *J Immunol* **24** 85, 1933.

nitely to substantiate the wisdom of this clinical judgment. The results of my own studies with tobacco will be treated in a subsequent publication. The second etiologic factor, probably the more striking, is the almost complete sex limitation of the disease. That the male is the more predominant victim was noted by clinicians<sup>15</sup> almost as early as the disease was identified as a specific clinical entity. Wider recognition of the symptomatology and a somewhat clearer knowledge of the pathology of the process have brought to light a much wider prevalence of thrombo-angitis obliterans than had previously been suspected. The consequent possibility of compiling statistics demonstrates conclusively that with the exception of isolated instances<sup>16</sup> in most of which the condition was unverified pathologically, the disease is definitely limited to the male. Horton and Brown,<sup>17</sup> reviewing the cases reported up to 1932, offered as a possible answer that women do have the disease, but in a much milder form than that occurring in men, and that the disease in women is overlooked because of the failure of development of the more serious sequelae. Even if this were true, however, the present proportion of less than 2 per cent of cases in women would not be seriously altered. Furthermore, this variation in degree between men and women remains to be explained. Is it possible that such disproportion may be founded on an endocrine basis? Let the question be transposed: translating thrombo-angitis obliterans in terms of ergot intoxication, what, if any, effect would an excess of available estrogenic substance have on the development of gangrene in the tail of a rat intoxicated with ergotamine?

A series of male and female rats was used, each rat receiving an initial intoxicating dose of ergotamine tartrate (25 mg per kilogram of body weight), and after an interval of twenty-four hours to allow thorough absorption of the alkaloid from the site of injection the administration of theelin in aqueous solution at the rate of 2 rat units per animal daily was begun. The injections of theelin were continued over a period of thirty days, at the end of which time all changes seemed to have ceased. As a further precaution the animals were observed for an additional twenty days. It was found that (1) in all rats, both male and female, receiving ergotamine alone, gangrene of the tail developed, (2) in

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15 Wwedensky, A. A. Ueber Arteritis Obliterans und ihre Folgen, *Arch f klin Chir* **57** 98, 1898.

16 Meleny, F. L., and Miller, G. G. A Contribution to the Study of Thrombo-Angitis Obliterans, *Ann Surg* **81** 976, 1925. Telford, E. D., and Stopford, J. S. B. Two Cases of Thrombo-Angitis Obliterans in Women, *Brit M J* **1** 1140, 1927. Trabaud, J., and Mredde, I. *Maladie de Leo Buerger chez une jeune fille musulmane*, *Bull et mem Soc med d hôp de Paris* **47** 579, 1931.

17 Horton, B. T., and Brown, G. E. Thrombo-Angitis Obliterans Among Women, *Arch Int Med* **50** 884 (Dec) 1932.

all male rats receiving both ergotamine and theelin gangrene developed comparable in extent to that in the animals receiving no theelin, (3) in female rats receiving both ergotamine and theelin gangrene did not develop, (4) in normal controls, male and female, no disturbances developed (tables 2 and 3)

The experiment was repeated, ergotamine being used in the ratio of 40 mg per kilogram of body weight, while in view of the results

TABLE 2—Results of Tests on the Females in the Four Series\*

	Series 1 Ergot amine, 25 Mg per kg	Series 2 Ergot amine, 40 Mg per kg	Series 3 Ergot amine, 60 Mg per kg	Series 4 Ergot amine, 100 Mg per kg	Total
Number of rats	30	30	30	30	120
Normal controls	10	10	10	10	40
Rats receiving ergotamine alone	10	10	10	10	40
Rats receiving ergotamine and theelin	10	10	10	10	40
Dosage of theelin, rat units daily	2	3	3	5†	
Gangrene in normal controls	0	0	0	0	0
Gangrene without theelin	10	10	10	10	40
Gangrene with theelin	0	0	0	2	2
Deaths	0	0	0	1	1

\* Ergotamine was given in a single dose at the beginning of the experiment injections of theelin were made over periods of thirty days, and the rats were observed for an additional twenty days thereafter

† Five rat units was the standard dose in series 4 In four rats, because of changes in the tails, 10 rat units was used daily

TABLE 3—Results of Tests on the Male Rats in the First Three Series\*

	Series 1 Ergotamine, 25 Mg per kg	Series 2 Ergotamine, 40 Mg per kg	Series 3 Ergotamine, 60 Mg per kg	Total
Number of rats	30	15	15	60
Normal controls	10	5	5	20
Rats receiving ergotamine alone	10	5	5	20
Rats receiving ergotamine and theelin	10	5	5	20
Dosage of theelin, rat units daily	2	5	8	
Gangrene in normal controls	0	0	0	0
Gangrene without theelin	10	5	5	20
Gangrene with theelin	10	5	5	20
Deaths	0	0	0	0

\* Ergotamine was given in a single dose at the beginning of the individual series The periods of injection of theelin and of observation were synchronous with those in the corresponding series of females, as indicated in table 2

in males in the preceding experiment the dose of theelin was increased to 3 rat units daily for females and 5 rat units daily for males The results in this series were identical with those in the previous study In a third series ergotamine was utilized in the ratio of 60 mg per kilogram of body weight, with doses of theelin of 3 rat units daily for females and 8 rat units daily for males Again the results were the same In all the rats except the females protected by theelin gangrene of the tail developed, in the protected females, no trophic lesions developed

A fourth series was studied, consisting only of females. Ergotamine was used in doses of 100 mg per kilogram of body weight. Four rats received ergotamine alone, six were given ergotamine and subsequent daily doses of 1 cc of physiologic solution of sodium chloride subcutaneously, and ten received the initial injection of ergotamine and thereafter theelin at the rate of 5 rat units daily. In this series it became evident early in the experiment that trouble would be encountered. In all the rats receiving ergotamine alone or accompanied by physiologic solution of sodium chloride, gangrene developed. However, in two of the group protected by theelin, gangrene quickly developed despite all efforts to thwart the process. These lesions, while appearing as early as those in the control group, had less than one-half the extent of those developing in unprotected animals (table 1). Two other animals showed evidence of vascular change in the tail in the form of pallor and mild cyanosis early in the course of the experiment. In these the dose of theelin was immediately doubled and was kept at that level for the remainder of the experiment. The pallor and cyanosis disappeared, and at the end of the study the rats in question could in no way be differentiated from the other animals protected by theelin. Thus in this series also the result was that in all ergotaminized rats unprotected by theelin, gangrene of the tail developed. In two of the animals protected by theelin, gangrene developed, while two others showed early vascular changes which promptly disappeared when the dose of theelin was doubled. The remaining rats demonstrated no changes.

#### ANALYSIS OF RESULTS

The patent fact derived from these experiments is that female rats previously intoxicated with ergotamine tartrate in amounts sufficient to produce gangrene of the tail were protected from the development of the gangrene by adequate amounts of theelin (table 3). While inspection of the results alone discloses this, the data for this series were subjected to the chi square test of probability<sup>18</sup>. This analysis demonstrates conclusively that the results are not attributable to the operation of chance alone. At first glance it would seem that theelin had no protective action on the male rats of the experiment (table 3). A mathematical analysis of the mean results, however, indicates that in series 1 there was a significant delay in the onset of trophic changes in the male rats receiving theelin as compared with the onset in males

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18 Chi square for the females of the four series, contrasting the results in those receiving ergotamine alone with the results in those receiving both ergotamine and theelin, on the basis of the development of gangrene of the tail, was 72.380925, the interpolation of which indicates that the possibility that these results were due to the operation of chance alone is less than 1 in 400,000,000,000.

not receiving theelin. This series was small, and the delay may disappear in a larger group. Moreover, the delay was not encountered in the later series of males. Considering the fact, however, that all the dosages of theelin used in the study were purely empirical, the discovery of this phenomenon in series 1 suggests the possibility that theelin may have some effect on the male, if administered in sufficiently large doses. Experiments testing this hypothesis are in progress.

In table 1 are compiled the mean times of appearance of the major trophic changes—pallor, cyanosis, blackness of the tail and demarcation of the gangrenous portion—together with the mean extent of the gangrenous process in the tails under increasing doses of ergotamine. Analysis of these means indicates a significant increase in the speed with which the trophic disturbances occur, varying directly with the increase of the dose of ergotamine. Such a relationship is not apparent in the extent of gangrene.

#### COMMENT

The mode of production of gangrene by ergot or its alkaloid, ergotamine, is not entirely clear. Cushny<sup>19</sup> stated that "the gangrene of ergot poisoning arises from the prolonged constriction of the vessels by the ergotoxine and ergotamine." In the next paragraph, however, one finds the statement "The ergot alkaloids do not act on the inhibitory junctions (of the sympathetic nervous system) at all, and while stimulating the motor myoneural junctions in small doses, paralyze them in large amounts." A similar description of the action of ergot and its alkaloids was offered by Dale,<sup>20</sup> Mendez,<sup>21</sup> Bastido<sup>22</sup> and Solis-Cohen and Githens.<sup>23</sup> The last two offered the following observation:

[In the cockscomb] There seems to be a contraction of all the vessels, most marked in the finer veins, leading to cyanosis. The vessels are dilated at first, and filled with brownish masses. Later, their walls [of the vessels], and finally the entire thickness of the comb, undergo hyaline degeneration, the vessels being filled with hyaline thrombi. A similar discoloration of the comb is produced by cantharides, which does not cause vasoconstriction, but it is not induced by other vasoconstrictors.

19 Cushny, A. R. *A Textbook of Pharmacology and Therapeutics*, ed 9, Philadelphia, Lea & Febiger, 1928, p 400.

20 Dale, H. H. On Some Physiologic Actions of Ergot, *J. Physiol.* **34** 163, 1906.

21 Mendez, R. Antagonism of Adrenalin by Ergotamine, *J. Pharmacol. & Exper. Therap.* **32** 451, 1928.

22 Bastido, W. A. *Materia Medica*, ed 3, Philadelphia, W. B. Saunders Company, 1933, p 657.

23 Solis-Cohen, S., and Githens, T. S. *Pharmacotherapeutics*, New York, D. Appleton & Company, 1928, p 1768.

Rothlin<sup>24</sup> expressed the opinion that the action of ergotamine is not on the motor junctions alone but that the inhibitory junctions are also involved. Further, it was stated by Heymans and Regniers,<sup>25</sup> as well as by Ganter<sup>26</sup> that ergotamine has a constant vasodilating effect in addition to its vasoconstricting effect, the one to manifest itself being dependent on the index of epinephrine in the blood at the time. Kaunitz<sup>26</sup> expressed the belief that the gangrene subsequent to ergot intoxication is due to the dystonic vascular condition, that is, there is a spasm of the arteries with dilatation of their terminal capillaries. He further suggested the possibility that the other amines in ergot, histamine, tyramine and choline may play a rôle in the phenomena observed. This possibility does not, of course, apply in the studies I am reporting, since ergotamine rather than the whole fungus was employed.

The nature of the interaction between the estrogenic factor and ergotamine is little understood. While knowledge of the action of ergotamine in toxic quantities is meager, knowledge of the action of theelin on the vascular system is virtually nil. Recent clinical studies indicate that some connection exists. In an analysis of 1,230 cases, Alvarez and Zimmermann<sup>27</sup> noted that sexually abnormal women have blood pressures that average considerably higher than those of women who are sexually normal and that a masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, thyroid disease and pelvic conditions requiring ovariectomy or hysterectomy are associated with a high average blood pressure. Conversely, Craicianu and his co-workers,<sup>28</sup> using estrogenic preparations, found that the intravenous injection of 100 rat units in dogs, especially in females, was followed by a drop in the blood pressure. Following the intravenous administration of 100 rat units to 100 human subjects a similar effect was noted, except in castrated women. Aymen,<sup>29</sup> contrariwise, in a careful

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24 Rothlin, E. Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, *J. Pharmacol. & Exper. Therap.* **36** 657, 1929.

25 Heymans, C., and Regniers, P. Sur l'action vasculaire et sympathetique de l'ergotamine et de l'ergotinine, *Arch. internat. de pharmacodyn. et de therap.* **33** 236, 1927.

26 Ganter, G. Ueber die Ausschaltung des vegetativen Nervensystems am Kreislauf, *Arch. f. exper. Path. u. Pharmacol.* **113** 129, 1926.

27 Alvarez, W. C., and Zimmermann, A. Blood Pressure in Women as Influenced by the Sexual Organs, *Arch. Int. Med.* **37** 597 (May) 1926.

28 Daniel, C., Craicianu, A., and Mavromati, L. Recherches cliniques des effets de la folliculine sur la pression artérielle chez l'homme, *Compt. rend. Soc. de biol.* **106** 997, 1931. Craicianu, A. Les effets vasculaires de la folliculine, *J. de physiol. et de path. gen.* **30** 305, 1932.

29 Aymen, D. The Treatment of Arteriolar Hypertension with Crystalline Ovarian Hormone (Theelin), *Am. J. M. Sc.* **187** 806 (June) 1934.



study of 10 patients, found that the daily administration of theelin over a period of three months, and in daily doses as high as 350 rat units was without any discernible effect on the blood pressure of hypertensive patients. It should be remarked in this connection, however, that while Alvarez and Zimmermann's study was statistical and was directed at what might be termed naturally existing conditions, Aymen's investigation was directed toward the study of the effect of therapy with theelin on a preexisting pathologic condition. Baecke<sup>30</sup> and Sicard<sup>31</sup> independently reported cases of thrombo-angitis obliterans in which the patient was relieved by therapy with estrogenic substance. Neither author offered a satisfactory explanation for the mechanism of the therapy. This work has not, to my knowledge, been corroborated by other clinicians. Kaunitz,<sup>6c</sup> reviewed the reports of such early observers as Noel (1710), Tessier (1783), Renauldin (1815) and Krynsky (1888) and cited their emphasis on the fact that in epidemic ergotism the gangrenous form of intoxication by the fungus failed, for the most part, to manifest itself in women. Such being the status of opinion as to the mode of operation not only of the estrogenic substance but also of ergotamine intoxication on the vascular system, I am forced to content myself at present with a simple record of my results, without offering any explanation of their causation.

The following observed phenomena are stressed

- 1 Thrombo-angitis obliterans has been recognized by investigators to be a sex-limited disease, attacking the male only, or, if one prefers the more conservative view advanced by Horton and Brown, its occurrence in the female is so mild as to escape notice.

- 2 In my present experiment, considering the gangrenous manifestations of ergotamine intoxication in the albino rat as a typical pathologic process, I found that females receiving sufficiently large doses of theelin are protected from the trophic disturbances which otherwise regularly follow intoxication with ergotamine tartrate.

I do not insist that there is a necessary connection between these phenomena. Nevertheless I think that it is not imprudent to indicate that herein lies the suggestion that in obliterative vascular diseases, notably in thrombo-angitis obliterans, there may be some underlying dyscrasia, possibly endocrine, and that the absence of or at least the notably milder form of the disease in the female may be associated with a protective action of the ovarian estrogenic factor.

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30 Baecke, L. Un cas de maladie de Leo Buerger (thrombo-angeste obliterante) traite par l'opotherapie ovarienne, *Bruxelles-med* 7 1086, 1927.

31 Sicard M. Sur la maladie de Buerger, *Bull et mem Soc med d hop de Paris* 51 443, 1927.

## SUMMARY

The similarity between thrombo-angitis obliterans and the gangrene of ergotamine intoxication is indicated, and the possibility of accepting the latter as a typical pathologic process on which to make further observations is discussed.

The gangrene of ergotamine intoxication was produced in the albino rat, and the pathologic process is described. The gangrene of the rat's tail can be induced regularly both in males and in females, with sufficiently large doses of ergotamine tartrate.

It was found that there is a significant increase in the speed with which trophic changes occur, varying directly with an increase in the dose of ergotamine tartrate. Such a relationship with regard to the extent of gangrene produced was not apparent in these studies.

The protective action of theelin against the gangrene of ergotamine intoxication was studied in a group of albino rats consisting of forty males and eighty females, exclusive of the normal controls.

Female rats initially intoxicated with ergotamine tartrate were completely protected against the gangrenous sequelae by sufficiently large daily doses of theelin.

In series 1, in which the amount of ergotamine tartrate administered was relatively small (25 mg per kilogram of body weight), male rats receiving theelin demonstrated a significant delay in the onset of trophic disturbances, as contrasted with male rats not receiving theelin.

The parallelism between the sex limitation of thrombo-angitis obliterans and the protection of the female rats from ergotamine gangrene by an excess of theelin is indicated.

It was noted that within this parallelism lies the suggestion that there may be in thrombo-angitis obliterans a basic etiologic disturbance which is possibly endocrine, and that the failure of the disease to manifest itself in women, or at least its presence in a form so mild as to escape clinical notice, may be associated with a protective action of the estrogenic principle of the ovary.

# METABOLISM IN UNDERNUTRITION

ITS CHANGES DURING TREATMENT BY HIGH CALORIC DIET

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In a recent publication<sup>1</sup> the treatment of undernutrition by high caloric diets was described. During the periods of gain in weight of the patients of the series studied in the hospital, observations were made of the changes which took place in several phases of metabolism. This report describes the observations which were made on the basal metabolism, nitrogen metabolism and efficiency of digestion.

## BASAL METABOLISM

Comparatively low levels of basal metabolism have long been recognized in association with undernutrition<sup>2</sup>. The total basal heat output is definitely reduced, and the relative deviations vary somewhat, depending on the use of standards of weight or body surface for the estimation of the basal metabolic rate in view of the unusual body proportions of these patients. The clinical significance which may be attached to observations of low basal metabolic rates is not easily determined. Many reports describe lowered metabolism in association with minor ailments<sup>4</sup> and even in persons with no discoverable pathologic condi-

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1 Strang, J M, and Evans, F A. Undernutrition and Its Treatment by Adequate Diet, *Ann Int Med* **7** 45, 1933

2 DuBois, E F. Basal Metabolism in Health and Disease, ed 2, Philadelphia, Lea & Febiger, 1927, p 207

3 (a) Benedict, F G. Basal Metabolism Data on Normal Men and Women with Some Considerations on the Use of Prediction Standards, *Am J Physiol* **85** 607, 1928. (b) Boothby, W M, and Sandiford, I. Basal Metabolism, *Physiol Rev* **4** 69, 1924

4 (a) McKinlay, C A. Concerning Limitations of the Clinical Significance of Low Basal Metabolic Rates, *Minnesota Med* **14** 713, 1931. (b) Thurmon, F M, and Thompson, W O. Low Basal Metabolism Without Myxedema, *Arch Int Med* **46** 879 (Nov) 1930

tion<sup>5</sup> The association of a rapid lowering of the metabolism with an acute loss in weight has been described in starvation<sup>6</sup> and following acute infection<sup>7</sup> In chronic undernutrition low metabolic levels have been recorded in association with specific diseases, such as diabetes,<sup>1b</sup> and also in less characteristic metabolic disorders<sup>8</sup> On the other hand, there are many reports of little or no change in the basal metabolism in simple, although chronic, undernutrition,<sup>9</sup> particularly when the observations are expressed in terms of basal metabolic rates

The mechanism whereby a drop in the level of the metabolism occurs in undernutrition has been much debated There appears to be no relation between lowering of the basal number of calories produced and lowering of the total body protein or body substance,<sup>10</sup> although low basal metabolism may be associated with a reduction in certain types of body protein<sup>11</sup> The conception that the lowered level of

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5 Wishart, G M The Variability of Basal Metabolism, *Quart J Med* **20** 193, 1926

6 (a) Aszodi, Z *Energieumsatz kleiner Tiere bei chronischer Unterernahrung*, *Biochem Ztschr* **152** 472, 1924 (b) Boothby, W M, and Bernhardt, H *Stoffwechselanalysen am Gesunden unter verschiedenen Bedingungen*, *Ztschr f klin Med* **116** 219, 1931 (c) Boothby, W M, and Sandiford, I<sup>3b</sup> (d) DuBois, E F<sup>2</sup> (e) Lusk, G The Physiological Effect of Undernutrition, *Physiol Rev* **1** 523, 1921 (f) Lusk, G The Science of Nutrition, ed 4, Philadelphia, W B Saunders Company, 1928, p 95

7 Gordon, H H, and Rabinowitch, I M Low Basal Metabolism Following Lobar Pneumonia Associated with Marked Undernutrition, *Am J M Sc* **180** 695, 1930

8 Berkman, J M Anorexia Nervosa, Anorexia, Inanition and Low Basal Metabolic Rate, *Am J M Sc* **180** 411, 1930 Lusk, G<sup>6e</sup>

9 (a) Benedict, F G, Miles, W R, Roth, P, and Smith, H M Human Vitality and Efficiency Under Prolonged Restricted Diet, publ 280, Carnegie Institution of Washington, 1919, p 1 (b) Krauss, E *Studien zur spezifisch-dynamischen Nahrungswirkung*, *Ztschr f klin Med* **112** 289, 1930 (c) Topper, A, and Mulier, H Basal Metabolism in Children of Abnormal Body Weight II In Underweight Children, *Am J Dis Child* **38** 299 (Aug) 1929 (d) Wang, C C, Kern, R, and Kaucher, M Metabolism in Undernourished Children IX A Study of the Basal Metabolism, Caloric Balance and Protein Metabolism During a Period of Gain in Weight, *Am J Dis Child* **38** 476 (Sept) 1929

10 (a) Brendle, E *Gaswechsel und Körperzusammensetzung*, *Arch f d ges Physiol* **226** 108, 1930 (b) DuBois, E F<sup>2</sup> (c) Lusk, G<sup>6e</sup> (d) Lusk, G<sup>6f</sup> p 174 (e) Wang, C C, Hawks, J E, Huddleston, B, Wood, A A, and Smith, E A The Influence of High and Low Protein Diet on the Basal Metabolism and the Chemistry of Blood and Urine in Normal Women, *J Nutrition* **3** 79, 1930

11 Deuel, H J, Jr, Sandiford, I, Sandiford, K, and Boothby, W M Study of Nitrogen Minimum, Effect of Sixty-Three Days of Protein-Free Diet on Nitrogen Partition Products in Urine and on Heat Production, *J Biol Chem* **76** 391, 1928

metabolism is due to primary or secondary hypofunction of the several endocrine glands, particularly the thyroid and adrenal glands, has met with considerable opposition<sup>12</sup> Nor does it appear to be a result of vitamin B deficiency<sup>13</sup>

The changes in the level of the metabolism which occur following a gain in weight are of particular importance for this study In general, previous studies have reported definite elevations of the basal metabolism coincident with increases in weight<sup>14</sup> However, with few exceptions, the rate of increase in weight far exceeds the rate of increase of the metabolism

The possible effect of the ingestion of large amounts of food per se on the basal metabolism must be kept in mind Observations have been reported which show an influence of high protein meals from fifteen to eighteen hours after ingestion<sup>15</sup> The influence of an excessive intake in general on heat production has been much debated, especially the conception of "luxus consumption"<sup>16</sup> Certain authorities, however, believe that the summation effect of the specific dynamic actions of the various food factors explains the increased heat output which follows an increase in food intake<sup>17</sup> and think that there is little or no effect of increased food intake on a truly basal determination

#### METHODS

The present report deals with observations of the basal metabolism of undernourished patients before and during treatment by high caloric diets The patients were under continuous observation in the pavilion for patients with metabolic disturbances The time intervals for this series of observations differ slightly from those for other observations on the same series of patients The weights employed were those noted on the morning of the basal determination and therefore differ somewhat from the figures for weight which appear elsewhere

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12 (a) Koehler, A E Differential Diagnosis Between Hypothyroidism and Hypoadrenalism, *J A M A* **91** 1457 (Nov 10) 1928 (b) Labbe, M, and Stevenin, H Le metabolisme basal dans l'alimentation insuffisante, *Presse med* **33** 400, 1925 (c) Moeller, E Quantitative Verhältnisse des Stoffwechsels bei Unter-ernahrung, *Klin Wchnschr* **3** 1575, 1924 (d) Thurmon, F M, and Thompson, W O<sup>4b</sup>

13 Mitchell, H H, and Carman, G G Effect of Excessive Amounts of Vitamine B on the Basal Metabolism of Rats of Different Ages, *Am J Physiol* **76** 385, 1926

14 Brendle, E<sup>10a</sup> Gordon, H H, and Rabinowitch, I M<sup>7</sup> Lusk, G,<sup>6f</sup> p 105 Moeller, E<sup>12c</sup> Thurmon, F M, and Thompson, W O<sup>4b</sup> Wang, C C, Kern, R, and Kaucher, M<sup>9d</sup>

15 Lusk, G<sup>6f</sup> Wishart, G M The Influence of Previous Muscular Activity and Other Factors on the Basal Metabolism, *Quart J Med* **20** 199, 1926

16 DuBois, E F<sup>2</sup> Labbe, M, and Stevenin, H<sup>12b</sup>

17 DuBois, E F<sup>2</sup> Lusk, G The Science of Nutrition, ed 4, Philadelphia, W B Saunders Company, 1928, p 388

The basal metabolism determinations were done at weekly intervals by the Tissot method as a routine at about 7 a m. The last meal was at 5 p m the preceding night, which gave an interval of at least twelve hours before the test. The calculations of the basal metabolic rate were based on the estimated surface area of the body. The normal standards of heat production of DuBois were used throughout.

In any long series of determinations occasional unusual variants are noted. In this series only those values were discarded in which definite technical errors were discovered. When two determinations were carried out in a week the figures recorded for that week are the averages of the two determinations and are so noted in the tables. No period of training could be secured before the institution of the high caloric diets. It is therefore possible that many of the initial determinations are unduly elevated. No basis for the evaluation of this possible error is apparent.

TABLE 1—*Basal Metabolism Before and After Gain in Weight*

Patient	Age, Years	Sex	Height, In	Weight, Kg	Initial Observation		Weeks	Final Observation		
					Heat Produc- tion, Calories per Hour	Basal Meta- bolic Rate		Weight, Kg	Heat Produc- tion, Calories per Hour	Basal Meta- bolic Rate
1	32	F	64	42.2	49.0	-5	13	52.5	53.9	-4
3	32	F	62½	38.6	48.5	+1	2	42.6	51.6	+2
4	22	F	62	43.1	50.3	-2	4	46.7	51.4	-4
5	28	M	66	49.0	54.7	-11	6	53.2	54.9	-14
6	35	M	68	43.0	63.3*	+9	6	57.7	77.0*	+16
7	24	F	62	40.8	52.4	+4	12	52.6	59.2	+6
8	20	F	62½	44.3	46.3*	-11	2	45.1	51.1*	-5
9	31	F	64¾	47.5	47.9	-13	2	49.3	47.9*	-13
10	23	F	66¼	45.3	49.7*	-10	4	48.1	48.5	-14
11	15	F	59	34.5	41.3	-21	3	36.7	44.3	-18
12	33	F	63	35.6	44.1	-7	8	42.0	45.2	-11
13	33	F	63	39.5	44.8	-10	3	42.7	45.5*	-11
14	26	F	64¼	50.3	58.4	+4	3	53.0	53.0	-8
15	25	F	67	46.7	64.9	+15	5	51.7	53.0	-10
16	25	F	67	54.8	60.0	-1	4	57.7	56.5	-8
17	22	F	64½	47.0	55.4	+1	2	48.7	54.1*	-3
18	33	M	66½	46.7	69.2*	+16	7	54.5	78.3*	+23
Average					52.9	-2	5		54.4	-6

\* Average of two determinations

## OBSERVATIONS

The observations of the basal metabolism made on seventeen patients at weekly intervals for an average of five weeks are recorded in table 1.

It may be noted that at the outset the average basal metabolic rate for the series was -2 per cent. The extreme range of values runs from -21 to +16 per cent, with eleven of the seventeen values falling between +10 and -10 per cent. These rates for undernourished patients correspond favorably with those for any series of normal persons.

If the final observations are compared with the initial observations without regard to duration or to change in weight, the average final heat production was 54.4, as contrasted with 52.9, calories per hour. The increase of 1.5 calories is equivalent to 2.8 per cent of the initial

level At the same time the increase in weight averaged 5.1 Kg, or 11.5 per cent, in the average period of five weeks Individual subjects showed changes ranging from a drop of 11.9 calories per hour, with consequent lowering of the basal metabolic rate of 25 per cent in three weeks, to an increase of 13.7 calories per hour and of the basal metabolic rate of 7 per cent in six weeks Eleven patients showed an increase in heat production, which was in most cases very slight and in four patients so small that the basal metabolic rate was reduced owing to the simultaneous increase in body surface Five patients showed a lower caloric output after an increase in weight and in consequence a much lower basal metabolic rate The detailed weekly observations of the basal metabolism have been omitted

The object of the present study is to note the metabolic changes which accompanied changes in weight The majority of our series of

TABLE 2—*Metabolism Changes of Patients Who Gained Five Kilograms or More*

Patient	Heat Production, Calories per Hour		Per cent age of increase	Body Surface, Sq Meters		Per cent age of increase	Basal Metabolic Rate Actual Body Surface		Ideal Body Surface, Sq Meters	Basal Metabolic Rate Ideal Body Surface		Change in Weight	
	Initial	Final		Initial	Final		Initial	Final		Initial	Final	Kg	Per cent age
	Observation	Observation		Observation	Observation		Observation	Observation		Observation	Observation		
1	49.0	53.9	10	1.41	1.54	9	-5	-4	1.64	-18	-10	10.3	24
6	63.3	77.0	22	1.49	1.69	13	+9	+16	1.84	-13	+5	14.7	34
7	52.4	59.2	13	1.37	1.51	10	+4	+6	1.55	-9	+3	11.8	29
12	44.1	45.2	2	1.30	1.39	7	-7	-11	1.61	-25	-23	6.4	18
15	64.9	53.0	-18	1.53	1.59	4	+15	-10	1.72	+2	-17	5.0	10
18	69.2	78.3	13	1.52	1.63	7	+16	+23	1.77	-2	+12	7.8	17
Average	57.1	61.1	7	1.44		8	+5	+3		-11	-5	9.3	22

patients did not remain in the hospital long enough to show important changes in body weight or surface If only those patients who gained 5 Kg or more are considered, much more striking figures are obtained

The six patients under consideration gained an average of 9.3 Kg—an increase of 22 per cent over the initial weights—in 8.5 weeks The average increase in body surface was 0.12 square meters, or 8 per cent The initial heat production averaged 57.1 calories per hour, which corresponds to an average basal metabolic rate of +5 per cent The final rate of heat production averaged 61.1 calories per hour The increase of 4 calories corresponds to 7 per cent of the initial level The average increase in body surface was 8 per cent, hence the change in the basal metabolic rate was very slight The observed increase in heat production, therefore, practically parallels the increase in body surface, while it is only one third of the increase in weight

From these data it might be considered that the increase in the metabolic level is influenced primarily by the body surface The possibility exists of an influence due to the great increase in the food intake

of these patients. The caloric intake for the several weeks has been reported elsewhere.<sup>18</sup> Certain of the figures for patients 1, 3, 10, 13 and 16 might be interpreted to indicate a fluctuation of metabolism with the food intake. The data for patients 9, 12, 15 and 18 could be interpreted as evidence either for or against such a fluctuation. The negative position is, however, clearly defined in the figures for patients 4, 5, 7, 14 and 17, which indicate a complete absence of relation between the caloric intake and the basal metabolism.

Similarly, the data for the protein intake, the total weight of intake, the total nitrogen metabolism, the level of the nitrogen metabolism, the total amount of nitrogen stored and the rate of storage of nitrogen were analyzed with respect to observed changes in heat production. The

TABLE 3—*Respiratory Quotients*

Patient	Ratio of Fatty Acid to Dextrose of Diet	Weeks												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1	0.61	0.730				0.824		0.891		0.909	0.880	0.852		0.865
3	0.68	0.822	0.795											
4	0.63	0.760	0.880	0.842	0.902									
5	2.44	0.710	0.744	0.780	0.770	0.740	0.740							
6	0.69	0.968	0.958	1.000	0.930	0.956	0.923							
7	0.61	0.890	0.836	0.927	0.798	0.874	0.883	0.864	0.872	0.908	0.892	0.882	0.868	
8		0.880	0.870											
9	0.65	0.826	0.837											
10	0.84	0.883	0.865	0.792	0.821									
11		0.814	0.902	0.820										
12	2.20	0.807	0.798	0.772	0.782	0.771	0.861	0.717	0.797					
13	3.19	0.713	0.731	0.752										
14	0.68	0.820	0.850	0.835										
15	0.75	1.000	0.788	0.820	0.808									
16	0.84	0.968	0.852	0.870	0.818									
17	0.65	0.760	0.855											
18	0.72	0.796	0.884	0.910	0.830	0.810	0.750	0.785						

detailed data have not been included in this report, but it may be stated that no relationship could be detected between these factors and their fluctuations and the changes in heat production.

The respiratory quotients which were observed are recorded in table 3.

There was a general tendency toward slightly higher values than are usually found for a similar series of normal persons. Characteristic changes in the respiratory quotients will be noted in the six patients who were studied for six weeks or longer.

In view of the many publications which describe the influence of the diet on the respiratory quotient, the figures for the fatty acid-dextrose ratio for the several patients are given (table 3, column 2). Patients 5, 12 and 13 were given high fat diets. The quotients for

18 Strang, J. M., and Cox, A. B. Analysis of High Caloric Diets in Relation to Weight Changes, *Ann Int Med* 7: 152, 1933.



these patients are definitely below those for the other subjects. It is, however, of interest that in patient 12 the respiratory quotient hovered around 0.8 while she received a diet containing 3,310 calories, with only 9.5 per cent from carbohydrate and 5.7 per cent from protein. Patient 13 had an average intake of 3,450 calories, with 5.3 per cent from protein and 4.8 per cent from carbohydrate. During the third week on this program the respiratory quotient was 0.752. In the remaining subjects the fatty acid-dextrose ratios of the diets ranged from 0.55 to 0.84. In these diets carbohydrate supplied from 27 to 36 per cent of the calories, and fat, from 54 to 66 per cent. The average total calories of all the diets was 3,320, which has been estimated as approximately 35 per cent above the total energy requirement for a day<sup>18</sup>. Also, it was estimated that of the weight gained, approximately one fourth was protein tissue and three fourths fatty tissue<sup>18</sup>. In view of the type of food and the probable nature of the weight gained, the general levels of the respiratory quotients are of especial interest. When the fat content of the diet is pushed to 85 per cent of the total calories, there appears to be slightly increased fat metabolism. A few patients appear to have utilized a relatively high percentage of carbohydrate. Patient 6 had the only consistently high respiratory quotient, and he ingested daily 5,090 calories derived in part from 399 Gm of carbohydrate and 326 Gm of fat. In the average diets, however, in which both carbohydrate and fat were given in amounts well over 200 Gm per day, the source of basal energy does not appear to differ greatly from the normal.

#### COMMENT

The initial observations made on this series of undernourished patients indicate that the basal metabolism falls within the limits of normal in proportion to the body surface. This fact is reflected in the observation of an average initial basal metabolic rate of  $-2$  per cent  $\pm 8$  per cent. The absolute heat production for the same patients was, however, lower than if their weight had been normal. Eight patients produced less than 50 calories per hour, the minimum being 41 calories per hour. A measure of this depression of rate is afforded by the calculation of the basal metabolic rates with the use of the ideal body surface in place of the actual body surface. By this form of expression it is seen that five patients had rates below  $-20$  per cent, and the average for the group was  $-15$  per cent, in contrast to the  $-2$  per cent already noted. It should, however, be clearly recognized that this calculation is not advanced as evidence contravening the principles underlying the standard methods of expression of the relative heat production. The chief merit of the calculation is that it affords one measure of the economy of energy exchange which prevails in undernourished persons. These observations support the conception of a

protective mechanism exhibited by a starved or undernourished body, which has been described by Lusk<sup>6e</sup>

The dietary treatment of undernutrition appears to exert a definite influence on the level of the basal metabolism. When all the patients are considered, the effect is obscured by the relative preponderance of the short periods of observations. If only those subjects are considered in whom important changes in weight occurred, the change in the basal level becomes more sharply defined. With the exception of one patient, whose initial level was unusually high, there was a distinct tendency for the metabolism to rise with an increase in body mass. The averages indicate that the rise in the level of the metabolism does not parallel the rate of the gain in weight, but is rather of the same order of magnitude as the rate of increase of the body surface.

An opinion which is frequently encountered is that undernourished persons show an increase in the level of the metabolism as a result of forced feeding. Although the food intake of all the persons in the series was increased abruptly, the average basal heat production of the group as a whole was changed but slightly, owing to the insignificant changes in heat production in the subjects studied for short periods. When the six patients who showed a significant change in weight are considered, the elevation of the basal metabolism appears to parallel the increase in body surface and does not follow the marked increase in food intake. The principle of a *luxus* consumption, therefore, does not appear to be applicable to the basal metabolism. Reference may be made to the estimations of the total heat output which were made for this series of patients<sup>18</sup>. In these calculations the only extra heat influence which was attributed to the excess food intake was the additional specific dynamic action of this excess food. As may be noted, the estimated gains in weight, which were dependent on this calculated total energy output, closely approximated the observed increases in weight. Our data could be interpreted in support of the statement of Lusk<sup>19</sup> that the heat loss in *luxus* consumption is essentially the additional specific dynamic action of the extra food intake.

Elevation of the basal metabolism has been attributed both to large meals and to high protein meals. Our observations have no bearing on the question of the influence of high protein meals, as our patients uniformly received moderate amounts of protein. With respect to large meals, our data fail to show that a significant elevation of the basal metabolism occurred immediately after the institution of diets furnishing from 3,000 to 5,000 calories daily. The observed changes developed more slowly. In this connection, attention may be called to the observations of the respiratory quotients. The intrinsic dangers of a discus-

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19 Lusk, G.,<sup>6f</sup> p. 53

sion and analysis of the respiratory quotients, especially of untrained subjects, are admitted. However, our subjects were tested under perhaps the most favorable circumstances and in most instances were thoroughly trained before the end of their stay in the hospital. The fact that the respiratory quotients, certainly in the later weeks, did not differ from those of a series of normal persons, suggests that the food influences in the basal state were no greater than in a series of normal persons. Our evidence is rather that the ingested food is promptly and efficiently handled by the gastro-intestinal tract, and that no residue is present to exert a specific dynamic action twelve hours after the evening meal. These observations are in harmony with the conclusions as to gastro-intestinal efficiency that were derived from the study of the fecal output.

### NITROGEN METABOLISM

The relationships which exist between the protein metabolism and proper nutrition have been subject to many investigations. The level of the protein intake necessary for adequate nutrition has been much debated. Low,<sup>20</sup> adequate<sup>21</sup> and optimum<sup>22</sup> protein diets have their advocates. Successful nutrition is apparently possible over a wide range of protein intake.<sup>20a</sup> Studies of undernutrition,<sup>23</sup> however, have indicated the association of a depressed protein metabolism with undernourished states.

### METHODS

In the observations here reported the nitrogen intake was estimated from the weights of the several foods. The figures for the protein content were based, for the most part, on the analyses of Atwater and Bryant<sup>24</sup> and a few unpublished analyses of our own. The figures recorded in the tables are the average intakes for the respective weekly periods.

The methods for the collection and storage of the urine and feces have been described elsewhere.<sup>25</sup> Aliquot portions of the thoroughly mixed seven day collections of urine and feces were analyzed in duplicate by the macro-Kjeldahl method. Except where specifically noted, all the analyses recorded in the tables are expressed in terms of grams of nitrogen per day for the several weekly

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20 (a) Mitchell, H. H. *The Physiological Effects of Protein*, J. Nutrition **1** 271, 1929. (b) Susskind, B. *Ein Stoffwechselfersuch bei knapper Ernährung*, Ztschr. f. d. ges. exper. Med. **72** 119, 1930.

21 Rubner, M. *Ueber den niedrigsten Eiweissverbrauch*, Ztschr. f. d. ges. exper. Med. **72** 99, 1930.

22 Slonaker, J. R. *The Effect of Different Per Cents of Protein in Diet*, Am. J. Physiol. **97** 15, 1931.

23 DuBois, E. F. *The Control of Protein in the Diet*, J. Am. Dietet. A. **4** 53, 1928. Lusk, G. <sup>6c</sup>

24 Atwater, W. C., and Bryant, A. P. *The Chemical Composition of American Food Materials*, U. S. Dept. Agric., bull. 28, 1906, p. 19.

25 Strang, J. M., McClugage, H. B., and Evans, F. A. *The Nitrogen Balance During the Dietary Correction of Obesity*, Am. J. M. Sc. **181** 336, 1931.

periods. For one patient (15) analyses of the stool were made for only four of the five weeks of observation, the average figure observed for the feces of the first four weeks was used in the estimation of the total nitrogen output for the fifth week. No correction of the average data for the variation in the individual periods of observation was attempted, although the periods ranged from three to fourteen weeks. The body weights employed in the calculations are the averages of the initial and final weights, except where otherwise noted.

## OBSERVATIONS

The average daily nitrogen intake for the series of eight patients was 10.96 Gm per day. According to the usual practice, an intake of 1 Gm of protein per kilogram of ideal weight was ordered. The total nitrogen intake varied from 6.85 to 18.48 Gm per day, and the intake per kilogram of ideal weight ranged from 0.115 to 0.259 Gm, with an average value of 0.172 Gm. The figures for the individual

TABLE 4—Average Daily Nitrogen Exchange

Patient	Intake				Output				
	Number of Weeks	Total	Per Kg of Actual Weight	Per Kg of Ideal Weight	Urine	Feces	Total	Per Kg of Actual Weight	Per Kg of Ideal Weight
1	14	6.85	0.144	0.115	4.68	0.99	5.67	0.119	0.095
5	6	9.25	0.178	0.144	7.64	0.66	8.30	0.160	0.129
6	6	18.48	0.368	0.259	8.65	2.13	10.78	0.214	0.151
10	4	8.93	0.193	0.149	6.71	0.89	7.60	0.164	0.127
14	3	11.20	0.215	0.193	8.14	1.53	9.67	0.186	0.166
15	5	8.90	0.179	0.142	4.91	1.30*	6.21	0.125	0.099
16	4	10.00	0.177	0.160	6.92	1.17	8.09	0.143	0.129
18	7	14.06	0.276	0.211	11.29	2.02	13.31	0.261	0.200
Average	6	10.96	0.216	0.172	7.37	1.34	8.70	0.171	0.137

\* Average for four weeks

weekly intakes, which are not included in this table, show some variation from week to week, although the majority of patients maintained a fairly uniform level throughout their stay. Certain patients whose initial level of intake was low showed no increase in this level, even after many weeks. Other patients showed the desired levels in the beginning, which continued. One subject showed an increase in nitrogen intake of from 9 to 15.5 Gm in four weeks, after which no increase in intake was permitted because of his failure to store nitrogen. The maximum intake was 18.48 Gm, or 0.368 Gm per kilogram, with a range of variation of from 18 to 18.9 Gm in six weeks.

The average total output of nitrogen in this series was 8.7 Gm per day. The extremes of variation were 5.67 and 13.31 Gm. Three patients showed no significant change in the average daily output during their entire stay. In two patients there was a drop in output of 20 per cent in fourteen weeks and 13 per cent in four weeks, respectively. Another patient showed a rise of 17 per cent in output. In one patient (6) the output rose from 8.86 to 12.49 Gm in five weeks, but never

equaled more than two thirds of his high intake. In patient 18, who had a thyrotoxic condition, the output of nitrogen differed from that of the other patients in that it rose sharply in four weeks to balance the intake at 16 Gm per day. On the average, the nitrogen output was about 80 per cent of the intake, with a range of from 59 to 95 per cent.

An expression of the output of nitrogen with reference to the body weight may be regarded as the level of the nitrogen output. The average level for the entire series was 0.172 Gm per kilogram of actual weight, with a range of from 0.119 to 0.261 Gm. With reference to the ideal body weight this value becomes 0.137 Gm per kilogram.

The changes in the level of output with change in weight are of considerable interest. Of the six patients with moderate outputs, two showed no alteration in the level because the rate of increase in weight paralleled a slight increase in the nitrogen output. Four patients showed a drop which in one case, in which a large increase in weight accompanied a decrease in the total output, amounted to 37 per cent of the initial level. Patient 6, who exhibited a 40 per cent rise in the total output in five weeks, showed no change in the level because of an equivalent large gain in weight. Patient 18 showed a marked relative increase in the nitrogen output—from 0.17 to 0.28 Gm per kilogram of body weight—in spite of a gain in weight of 9.1 Kg.

#### COMMENT

Many instances of a low protein intake associated with undernutrition have been reported.<sup>23</sup> An attempt was made to determine the approximate nitrogen intake of several of our subjects which obtained prior to the period of treatment. The figures obtainable were undoubtedly influenced by the residence in the hospital and therefore probably fail to indicate exactly the preexisting intake. Nevertheless, a distinct impression was received that many of our patients had been securing inadequate amounts of protein prior to the periods of study.

The amount of dietary protein necessary for the treatment of undernutrition obviously is related to the total diet. In the treatment of undernourished children amounts varying from 1.1<sup>26</sup> to from 2 to 4 Gm<sup>27</sup> per kilogram of body weight have been used, with considerable success. The majority of our patients were given 1 Gm of protein, or 0.16 Gm of nitrogen, per kilogram of ideal weight. The average

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26 Parsons, J. P. Nitrogen Metabolism of Children, *Am J Dis Child* **39** 1221 (June) 1930.

27 Wang, C. C., Hawks, J. E., and Kaucher, M. Metabolism of Undernourished Children. VII. Effect of High and Low Protein Diets on the Nitrogen and Caloric Balance of Undernourished Children, *Am J Dis Child* **26** 1161 (Dec.) 1928.

actual intake closely approximated this figure. It may be noted that this average figure is about 30 per cent higher (0.21 Gm per kilogram) when based on the actual weight. It would appear, therefore, that our patients, on the whole, were on diets of moderate nitrogen content, in fact, somewhat less than that in other series which have been reported.

The absorption and utilization of nitrogen by the gastro-intestinal tracts of undernourished patients is apparently normal, provided that the remaining dietary factors are properly controlled.<sup>28</sup> However, an important loss of nitrogen in the stools has been reported in undernourished subjects under unfavorable conditions.<sup>29</sup> The details of our studies of nitrogen absorption are given later, but it may be stated at this point that no abnormality of this factor was detected in our series.

The total daily nitrogen output of our patients both at the outset and after periods of dieting was definitely below that found in persons of normal weight.<sup>30</sup> Our observations provide no evidence of a waste of nitrogenous material as an explanation of the development or persistence of undernourished states. They tend to show the protective mechanism of starvation (Lusk) with respect to the nitrogen metabolism. If the change in weight is reversed and undernourished patients are fed, is this mechanism reversed? A number of studies bearing on this point<sup>31</sup> indicate that the rise in the nitrogen metabolism following an increase in intake is much delayed and is of a much smaller magnitude than the rise in the intake. The results in our patients were consistent with this experience. Not only was the caloric intake increased by 50 per cent or more, but the nitrogen intake remained, on the average, 25 per cent greater than the output. The majority of patients exhibited little or no increase in the nitrogen output over the

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28 (a) Coleman, W., and DuBois, E. F. The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, *Arch Int Med* **14** 168 (Aug.) 1914. (b) DuBois, E. F. The Absorption of Food in Typhoid Fever, *ibid* **10** 177 (Sept.) 1912. (c) Wang, C. C., Hawks, J. E., and Hays, B. B. Metabolism of Undernourished Children. V Protein Metabolism, *Am J Dis Child* **35** 968 (June) 1928. (d) Whitacre, J., Willard, A., and Blunt, K. The Influence of Fiber on Nitrogen Balance and on Fat in the Feces of Human Subjects, *J Nutrition* **2** 187, 1929.

29 Rubner, M., quoted by Lusk, G.<sup>6e</sup>

30 Beard, H. Protein Intake of Medical Students, *Am J Physiol* **82** 577, 1927. Dennis, W., and Borgstrom, P. A Study of the Effect of Temperature on Protein Intake, *J Biol Chem* **61** 109, 1924.

31 (a) Van Hoesslin, H., quoted by Lusk, G.<sup>6e</sup> (b) Boothby, W. M., and Bernhardt, H.<sup>6b</sup> (c) Rubner, M. Ueber den Stoffwechsel bei Unterernahrung, *Ztschr f d ges exper Med* **72** 123, 1930. (d) Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M.<sup>9a</sup> (e) Deuel, H. J., Jr., Sandiford, I., Sandiford, K., and Boothby, W. M.<sup>11</sup> (f) Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration. IV Malnutrition and the Serum Proteins, *J Clin Investigation* **8** 577, 1930.

several weeks of study. The single variant from the general pattern (in patient 18) possibly is due to the underlying pathologic condition, thyrotoxicosis.

The nitrogen metabolism as reflected by the level of the nitrogen output was relatively low in the majority of the patients in our series, averaging 0.13 Gm per kilogram of ideal weight or 0.16 Gm per kilogram of actual weight. Many reports have appeared which discuss the minimum level that may be obtained. The influence on the minimum level of the total caloric intake has been well established by studies of both starvation<sup>6f</sup> and underfeeding.<sup>9a</sup>

The minimum "wear and tear" nitrogen was estimated many years ago as 0.044 Gm per kilogram of body weight.<sup>29</sup> Levels of 0.024 Gm have been maintained for short periods.<sup>11</sup> According to certain studies of American diets,<sup>30</sup> the normal nitrogen exchange is about 0.16 Gm per kilogram of ideal weight (in these subjects, the observed weights). In comparison with these standards, our subjects showed levels far above the minimum but at the same time somewhat lower than their ideal nitrogen exchange.

The marked capacity of undernourished subjects for storing nitrogen has been repeatedly described.<sup>32</sup> The avidity for storing nitrogen appears to bear some relation to the degree of undernutrition.<sup>33</sup> However, it is important to maintain an adequate caloric intake as well as an increased nitrogen intake in order to produce this phenomenon. In fact, in many reports it is not possible to distinguish between the influence of feeding increased amounts of protein and that of an increased caloric intake. All the patients of this series had a positive nitrogen balance. On the average, they stored 2.26 Gm per day. Although the extremes ranged from 0.77 to 0.75 Gm, the majority stored from 1 to 3 Gm per day. It is noteworthy that although they received only moderate amounts of protein, yet they maintained a relatively large positive nitrogen balance because the output increased but little over the initial level.

The rate of storage of nitrogen does not appear to be related directly to the level of the nitrogen intake. The amounts stored varied from 5 to 41 per cent (average, 19 per cent) of the nitrogen taken in, but bore no direct relation to the magnitude of the intake. Obviously the caloric intake has some influence on the nitrogen storage. However, this relationship is not susceptible of simple expression, either in terms of the amount of nitrogen stored per hundred calories of total intake.

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32 (a) Boothby, W. M., and Bernhardt, H.<sup>6b</sup> (b) Lusk, G.<sup>6e</sup> (c) Van Hoesslin, H. quoted by Lusk, G.<sup>6e</sup> (d) Wang, C. C., Hawks, J. E., and Kaucher.<sup>27</sup> (e) Rubner, M.<sup>31c</sup>

33 Rubner, M.<sup>31c</sup> Van Hoesslin, H.<sup>32c</sup> Wang, C. C., Hawks, J. E., and Kaucher, M.<sup>27</sup>

or in terms of the amount stored per hundred extra calories of intake<sup>18</sup> With respect to the body mass, it may be seen that the nitrogen was stored at the average rate of 0.045 Gm per kilogram per day. Again the rate of storage did not parallel the size of the patient or the degree of undernutrition.

In contrast to the preceding discussion of the rate of nitrogen storage it is of interest to note the change in the total nitrogen content of

TABLE 5—*Relative Amount of Nitrogen Stored*

Patient	Nitrogen Stored per Day, Gm	Ratio of Nitrogen Stored to Nitrogen Intake, Gm	Caloric Intake	Nitrogen Stored per 100 Calories of Intake, Gm	Excess Calories*	Nitrogen Stored per 100 Calories, Gm	Nitrogen Stored per Kg of Actual Weight, Gm	Average Kg Under weight	Nitrogen Stored per Kg Under weight, Gm	Average to Per centage Under weight	Ratio of Nitrogen Stored to Per centage Under weight, Gm
1	1.18	0.17	2,790	0.042	614	0.19	0.025	12.2	0.10	21	0.056
5	0.95	0.10	2,980	0.031	897	0.10	0.018	12.5	0.08	20	0.047
6	7.70	0.41	5,090	0.152	2,315	0.83	0.153	21.1	0.37	30	0.260
10	1.33	0.15	3,200	0.044	1,206	0.11	0.029	13.1	0.10	22	0.060
14	1.53	0.13	3,060	0.050	911	0.16	0.029	6.0	0.26	11	0.139
15	2.69	0.30	3,260	0.082	1,022	0.23	0.054	12.9	0.21	22	0.122
16	1.91	0.19	3,310	0.077	1,078	0.18	0.034	6.0	0.32	10	0.191
18	0.75	0.05	4,790	0.016	1,976	0.04	0.015	15.7	0.05	24	0.031
Aver	2.26	0.19		0.079		0.17	0.045		0.18		0.110

\* Strang and Cox<sup>18</sup>

TABLE 6—*Total Amount of Nitrogen Stored*

Patient	Number of Days	Nitrogen Stored per Day, Gm	Total Increase in Nitrogen, Gm	Initial Nitrogen Content of Body, Gm	Per centage of Increase of Body Nitrogen	Increase in Body Weight, Kg	Nitrogen Stored per Kg of Weight Gained, Gm	Total Protein Tissue Formed, Kg	Ratio of Protein Tissue to Weight Gained, Per centage
1	95	1.18	112.1	1,260	8.8	11.4	9.8	2.8	24
5	42	0.95	39.9	1,490	2.6	4.8	8.3	1.0	21
6	42	7.70	323.4	1,240	26.0	17.7	18.2	8.1	45
10	28	1.33	37.2	1,340	2.8	4.3	8.6	0.9	22
14	21	1.53	32.1	1,480	2.1	5.4	5.9	0.8	15
15	35	2.69	94.2	1,400	6.7	6.2	15.2	2.4	38
16	28	1.91	53.5	1,620	3.3	4.9	10.9	1.3	27
18	49	0.75	36.8	1,390	2.6	9.1	4.0	0.9	10
Average	43		91.1	1,400	6.6	8.0	10.1	2.3	25

these patients. The total additions of nitrogen, obtained by multiplying the average amount stored daily by the number of days, appears in column 4 of table 6. On the average, our patients stored 91 Gm in forty-three days. The maximum amount stored was in patient 6, who retained 323 Gm of nitrogen in forty-two days. This patient may be compared with the patient described by Lusk,<sup>19</sup> who stored 124 Gm in four weeks. Lusk estimated that for 1 Kg of average body weight the nitrogen content is 30 Gm. On the basis of this estimation, our series of patients had initial nitrogen contents ranging from 1,240 to



1,620 Gm, with an average of 1,400 Gm. The observed increase in the nitrogen content, therefore, constitutes, on the average, 7 per cent of the initial nitrogen content, with a variation of from 2 to 26 per cent.

The relation of the increase in body nitrogen to the increase in weight is recorded in column 8 of table 6. It may be noted that while the patients stored 91 Gm of nitrogen they gained 8 Kg. One kilogram of the weight gained corresponds to but 10 Gm of nitrogen, in contrast to the figure of Lusk. This observation may be interpreted to suggest that in the weight gained the proportion of fat to protein is far in excess of the relative amounts of these substances in the average body—a point of view which is in accord with everyday experience, as well as with calculations which have been reported elsewhere<sup>18</sup>. Furthermore, if it is assumed that protein tissue contains 25 per cent solids and 75 per cent water, 1 Gm of nitrogen corresponds to 25 Gm of protein tissue. On the basis of these assumptions, the weight gained by our patients as a whole was composed of 75 per cent fat and 25 per cent protein tissue. In individual cases the proportion ranged from 10 to 45 per cent protein and from 55 to 90 per cent fat. It might be stated, therefore, that, whereas in patients 14 and 18 the weight gained was chiefly fat tissue, in patient 6 roughly half of the weight gained was protein tissue.

#### SUMMARY

Observations on undernourished patients afforded no evidence that nitrogen is dissipated by any peculiar mechanism of nervous, hormonal or other origin. The data indicate a normal or even conservative handling of nitrogenous substances. The total nitrogen output tended to be distinctly lower than the values encountered in a series of patients of normal weight. In proportion to the actual weight of the subjects, the nitrogen levels were within the limits of normal.

In the course of dietary treatment, although the nitrogen intake was not particularly large, the patients stored nitrogen avidly. The nitrogen content of the patients increased by 7 per cent in the relatively short period of six weeks. Of greater importance, however, is the fact that even after long periods of a positive nitrogen balance the level of the nitrogen output did not rise. These observations serve to emphasize the teaching of Rubner and Lusk relative to the great capacity for nitrogen storage which is associated with serious grades of under-nutrition.

The rate at which nitrogen is stored by any given subject does not appear to be predictable. In our series of patients no simple relationships could be noted between the rate of storage and the several factors of the total intake, nitrogen intake, nitrogen output, degree of under-nutrition or change in weight.

## EFFICIENCY OF DIGESTION

In the treatment of undernutrition by high caloric diets it is of importance to determine the utilization of the ingested food. According to many popular notions, thin persons are unable to handle large quantities of food. Functional abnormalities of the gastro-intestinal tract have been noted in association with undernutrition<sup>34</sup>. However, several studies have been reported which showed a normal capacity of the gastro-intestinal tract for handling large food intakes in both acute and chronic forms of undernutrition<sup>35</sup>. The opinion has been stated that it is not possible to overtax the efficiency of the digestive system and that the handling of a food intake regulated by the appetite is no better than that with forced feeding<sup>36</sup>. The observations here recorded in which the relation of the feces to food is employed as the index of digestive efficiency were made on nine patients during their several periods of gain in weight by means of high caloric diets.

## METHODS

The methods of determining the food intake have been described elsewhere<sup>18</sup>. Stools were collected in bed pans separate from urine. When the specimens were mixed, the fluid portion was immediately removed and regarded as urine. The feces were transferred to previously weighed wax cartons, which were kept in a refrigerator. The total collection for each twenty-four hours was weighed on a balance to the nearest gram. The twenty-four hour specimens were transferred daily to the laboratory, where they were stored for seven days. Some loss of water through the wax paper occurred in this period, hence the calculations of the total weight and water content are based on the original records of weight determined in the ward. The dates for the collection of feces correspond to those for food intake. It is recognized that this procedure admits a certain lack of correspondence between feces and food. The error, however, is practically negligible in view of the use of seven day averages and of the relative uniformity of the diet from week to week.

Analyses were performed on aliquot portions of the thoroughly mixed collections for each week. For the determination of the total solids, a portion was evaporated to constant weight over a steam bath. Ninety-five per cent solution of alcohol was added from time to time to facilitate dehydration. The water content was estimated by the difference in weight before and after dehydration. Determinations of the nitrogen were carried out by the macro-Kjeldahl method. Determinations of the fat were made for only four patients. The total ether-soluble

34 Rupp, A., and Schlutz, F. W. Motility of the Empty Stomach in Normal and in Malnourished Asthenic Children, *Am J Dis Child* **39** 241 (Feb) 1930.  
Hoelzel, F., and Kleitman, N. Some Conditions Affecting Subjective and Objective Manifestations of Hunger, *Arch Int Med* **39** 710 (May) 1927.

35 DuBois, E. F.<sup>28b</sup> Wang, C. C., Hawks, J. E., and Kaucher, M.<sup>27</sup> Wang, C. C., Kern, R., and Kaucher, M.<sup>2d</sup>

36 Childrey, J. H., Alvarez, W. C., and Mann, F. A. Digestion Efficiency with Various Foods and Under Various Conditions, *Arch Int Med* **46** 361 (Sept) 1930.

matter was estimated as fat. The figures in tables 7, 8 and 9 are the averages of the several weekly observations for each patient, expressed in terms of grams per day.

## OBSERVATIONS

Careful records of the fecal output are available for nine patients of the series. These have been described elsewhere.<sup>37</sup> Analyses of the fat were carried out on only four patients of the series. These observations are recorded in table 7.

The average weight of the output was 165 Gm. with a range of from 80 to 247 Gm. per day. The weekly figures, which are not given in tables 7, 8 and 9, show a rather striking uniformity of output in a given person from week to week.

The total solids in the feces averaged 31 Gm. per day. Not only was this figure constant for a given subject from week to week, but

TABLE 7—*Analysis of Feces*

Patient	Number of Weeks	Total Weight, Gm	Solids, Gm	Per centage of Solids	Water, Gm	Per centage of Water	Nitrogen, Gm	Per centage of Nitrogen	Fat, Gm	Per centage of Fat
1	6	133	19	14	114	86	0.99	0.7		
5	6	136	57	42	79	58	0.66	0.4	42.7	31.0
6	6	242	37	15	205	85	2.13	0.9	2.3	0.9
10	4	80	22	28	58	72	0.89	1.1		
14	3	247	28	11	219	89	1.53	0.6		
15	4	182	32	18	150	82	1.30	0.7	8.0	4.4
16	4	122	22	18	100	82	1.17	0.9	0.7	0.5
17	1	107	19	19	88	81	0.94	0.9		
18	7	239	45	19	194	81	2.02	0.8		
Average		165	31	20	134	80	1.29	0.8		

there was markedly little deviation from this average in all the subjects.<sup>19</sup> The figure represents 20 per cent of the total weight of the fresh feces. This percentage, however, varies somewhat more than the dry weight, owing to the greater variations in the water content. One patient averaged 89 per cent water for three weeks without having had diarrhea or having taken cathartics. Another patient averaged only 58 per cent water over a period of six weeks. In the majority, however, the percentage of water ranged from 80 to 85.

The nitrogen content of the stools averaged 1.29 Gm. per day. The lowest value—0.66 Gm.—was obtained for the patient whose stools had a high fat content. The high values—2.13 and 2.02 Gm.—were obtained for the two patients on high caloric and relatively high protein diets. Although these high values are somewhat above the normal limits described by DuBois<sup>28b</sup> (1.8 Gm.), the average value closely approximates the average for his series of patients with typhoid. It is of considerable interest to note that the nitrogen constitutes less than 5 per

37 Strang, J. M., and Cox, A. B.<sup>18</sup> Strang, J. M., and Evans, F. A.<sup>1</sup>

cent of solids of the stool. This figure is somewhat lower than the several ratios recorded by Lusk.

The fat content of the feces of three patients who received ordinary mixed diets ranged from 0.7 to 8 Gm. In one patient who ate 274 Gm of fat (86 per cent of the 3,000 calories) the fecal fat reached 43 Gm a day, or 16 per cent of the ingested fat.

Although the absolute figures for the composition of the feces are of interest, their significance becomes greatly increased when viewed in relation to the corresponding food intakes. These facts are summarized in table 8.

In the first two columns of table 8 are recorded the average daily weights of the food intake and of the feces, which are 1,926 and 165

TABLE 8—*Relation of Components of Feces to Various Food Factors*

Patient	Weight of Food, Gm	Weight of Feces, Gm	Ratio of Weight of Feces to Weight of Food, Per centage	Food Solids, Gm	Fecal Solids, Gm	Ratio of Fecal Solids to Food Solids, Per centage	Food Nitro gen, Gm	Fecal Nitro gen, Gm	Ratio of Fecal Nitro gen to Food Nitro gen, Per centage	Total Weight of Intake, Gm	Ratio of Fecal Nitro gen to Intake, Per centage	Ratio of Fecal Nitro gen to Fecal Solids, Per centage
1	1,557	133	8.5	465	19	4.1	6.85	0.99	14.5	3,345	0.029	5.2
5	1,303	136	10.4	382	57	14.9	9.04	0.66	7.3	2,994	0.022	1.2
6	2,521	242	9.6	841	37	4.4	18.48	2.13	11.5	4,311	0.049	5.7
10	1,791	80	4.5	500	22	4.4	8.93	0.89	10.0	2,403	0.037	4.0
14	2,240	247	11.0	506	28	5.5	11.20	1.53	13.7	3,953	0.038	5.5
15	1,760	182	10.3	521	32	6.1	8.67	1.30	15.0	3,091	0.042	4.1
16	1,728	122	5.6	521	22	4.2	10.00	1.17	11.7	2,771	0.042	5.3
17	1,730	107	6.2	434	19	4.4	12.00	0.94	7.8	2,837	0.033	5.0
18	2,700	239	8.9	776	45	5.8	14.06	2.02	14.4	4,860	0.041	4.5
Average	1,926	165	8.3	549	31	5.8			11.8		0.037	4.5

Gm, respectively. The fecal output, therefore, constitutes 8.3 per cent of the food intake. However, there is a considerable range of individual variation—from 4.5 to 11 per cent. A somewhat different impression of the relation of the fecal output to the food intake is obtained if the relation between the fecal solids and the food solids is determined. From columns 5 and 6 of table 8 it may be noted that the food solids averaged 549 Gm and the fecal solids, 31 Gm. The fecal solids correspond to 5.8 per cent of the food solids. The significance of this relation is perhaps emphasized by the relatively slight variations in eight patients—from 4.1 to 6.1. The single large deviation occurred in patient 5, who received a very high fat diet and who produced concentrated stools in which 75 per cent of the solid material was fat. If this single value is omitted from the calculations, the average becomes  $4.8 \pm 0.6$  (12 per cent), which is a variation only half as great as that for the ratio of the fecal weight to the weight of the food.

The nitrogen in the stool was 11.8 per cent of the nitrogen intake. The individual variations ranged from 7.3 to 15 per cent, with an average deviation of 2.4 per cent, or 20 per cent. The nitrogen output appears to be influenced to some extent by the total weight of the intake, as shown in column 12. It may be seen that the nitrogen output corresponds to  $0.037 \pm 0.006$  per cent of the total weight of the intake. These data suggest that although the nitrogen in the stools is influenced by the nitrogen intake, it is also affected by the total mass of the intake.

TABLE 9—*Relation of Fecal Solids to Food Intake*

	Patient	Number of Weeks	Intake of Food, Calories	Food Solids, Gm	Fecal Solids, Gm	Ratio of Fecal Solids to Food Solids, Percentage
2,000 Calorie Diets	1	2	2,150	358	27	
	Average			358	27	7.5
2,500 Calorie Diets	15	1	2,410	384	30	
	17	1	2,570	434	19	
	Average		2,490	409	25	6.1
3,000 Calorie Diets	1	4	2,920	490	18	
	5	6	2,980	382	57	
	10	3	3,090	485	21	
	14	3	3,060	506	28	
	16	2	3,030	482	20	
	Average		3,020	469	29	6.2
3,500 Calorie Diets	10	1	3,510	545	23	
	15	3	3,520	566	33	
	16	2	3,600	560	24	
	18	1	3,710	603	27	
	Average		3,580	568	27	4.8
4,500 Calorie Diets	18	2	4,400	707	40	
	Average		4,400	707	40	5.7
5,000 Calorie Diets						
	6	6	5,090	841	37	
	18	4	5,250	854	44	
	Average		5,170	848	40	4.7

This observation supports the statement of Whitacre and his associates<sup>28d</sup> that a high proportion of bulk in the diet tends to reduce the utilization of nitrogen. If the fecal nitrogen is compared with the fecal solids it is found that the nitrogen constitutes 4.5 per cent of the solids. If the single variant—that shown by patient 5—is omitted, eight subjects averaged  $4.9 \pm 0.5$  per cent. This average deviation of only 10 per cent suggests that although the nitrogen intake and the bulk of the food affect the fecal nitrogen, the relation of the fecal nitrogen to the fecal solids is even more close.<sup>38</sup>

The data just given describe the average relations of the food to the feces for the entire periods of observation. An attempt was made to correlate the fecal output with the several levels of food intake. In table 9 the individual dietary periods are subdivided to indicate the number of weeks during which each patient maintained a given level of intake. The figures recorded for the intake are the averages of the several weeks, not necessarily consecutive, at which the level was maintained.

Five persons maintained intakes of 3,000 calories for eighteen weeks. During this period the fecal solids averaged 62 per cent of the food solids. For two week periods at levels of 2,000 and 2,500 calories the relations were 61 and 75 per cent. On the other hand, when the higher ranges of intake were reviewed, it was found that for seven weeks at the 3,500 caloric level the ratio was 48 per cent, and for two weeks at the 4,500 caloric level, 57 per cent and, particularly, for ten weeks at the 5,000 caloric level, 47 per cent. If these ratios are compared with the average for the entire group for all the periods—58 per cent—it will be noted that, contrary to the usual presumption, the ratios are definitely smaller at the higher levels of intake and definitely larger at the lower levels of intake. Such data supply no grounds for the assumption that large food intakes are inadequately handled by the body.

#### SUMMARY

The importance of a detailed consideration of the relation of the food intake to the fecal output lies in the information relative to the digestion and absorption of food. It is recognized that the feces consist of substances other than the mere residue of ingested food. Nevertheless, these observations provide the only measure at present available for the estimation of the efficiency of digestion. If only a portion of the feces represents the result of failure of digestion and absorption, any conclusion reached by the use of the total values observed will be understatement rather than overstatement of the efficiency of digestion. From the figures relating to the total weights of the food and feces it may be considered that our patients digested and absorbed 92 per cent of the food provided. These figures are similar to the generally accepted values for absorption when calculated in this way. If, however, the relation of the food solids to the fecal solids is considered as the index of absorption, the absorption for eight patients averaged 95 per cent, whereas the single patient with the high fat diet absorbed only 85 per cent of his intake. These figures for the average absorption of a general mixed high caloric diet are well within the recognized limits for ordinary diets. If, carrying the analysis one step further, a comparison is made of the digestive efficiency at the several levels, it may be seen that whereas the average absorption for all levels was 94 per

cent, the higher intakes were more efficiently handled and the lower intakes less efficiently handled than in the average person. It may, therefore, be stated that these studies supply no evidence that the gastrointestinal tracts of thin persons are in any way inferior to those of more robust persons, nor is there any indication of an unusual loss of energy by this route. Rather it is suggested that the digestive and absorptive capacity of a person are adequate for any food intake which he can be induced to ingest.

### GENERAL CONCLUSIONS

Studies of the basal metabolism, nitrogen metabolism and efficiency of digestion of patients with severe degrees of undernutrition showed no abnormalities in these factors which could cause the initiation or persistence of such states of undernourishment.

The changes in these three factors which were observed as a result of either the high caloric intake or the increases in weight dependent thereon indicated no new principles of metabolism which might militate against the successful treatment of undernutrition by dietary measures.

# FAT TOLERANCE IN HYPERTHYROIDISM

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Hyperthyroidism is accompanied by an increased metabolism which causes the body to burn up first its available carbohydrates, then its superfluous fat and later its protein. The exact source of the energy that goes into the production of the excess heat is obscure. Carbohydrates are, in normal persons, an important source of heat production. In hyperthyroidism the glycogen content of the liver is greatly depleted, if not completely exhausted, as was shown by Cramer and Krause,<sup>1</sup> Kuriyama,<sup>2</sup> Fukui,<sup>3</sup> and Coggeshall and Greene.<sup>4</sup> Yet in this condition Denis, Aub and Minot,<sup>5</sup> Gardiner-Hill, Brett and Smith,<sup>6</sup> and Sanger and Hun<sup>7</sup> observed reduced tolerance for sugar. Boothby and Sandiford,<sup>8</sup> as a result of extensive experiments, concluded that "there is no measurable increase in the endogenous protein metabolism in exophthalmic goiter, therefore it can not be the cause of the increased basal metabolism in this disease."

Although the oxidation of fat produces the largest amount of heat in the normal person, little attention appears to have been paid to this source of energy in hyperthyroidism. However, it has been assumed that the gradual loss of fat which results from the administration of thyroxin or of thyroid extract is caused to a large extent by the generally greater expenditure of energy and particularly by the increased muscular movement. But Abelin and Kursteiner<sup>9</sup> brought forward evidence that the thyroid secretion may also exercise a direct

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effect on fat metabolism, since they observed that large doses of thyroid extract cause the disappearance of a considerable proportion of the body fat of rats within from twenty-four to seventy-two hours, that is, before the general metabolic effect of the hormone was detectable. Kommerall<sup>10</sup> produced an increase of 30.5 per cent in the basal metabolism of dogs by feeding dried thyroid, 31.3 per cent of this increase was due to increased protein metabolism, while 68.7 per cent was due to increased fat metabolism.

Most investigators have reported a decrease in the fat content of the blood in hyperthyroidism. Raab<sup>11</sup> stated that the subcutaneous administration of thyreiodine to dogs in no way influences the fat content of the blood. Sakurai<sup>12</sup> found that a single dose of thyroid emulsion decreased the fatty acid and cholesterol values of the blood of rabbits, while repeated injections increased the values. Thyroidectomy was followed by an increase in the blood fats, which could be prevented temporarily by the injection of thyroid emulsion. Silberstein, Gottdenker and Geiger<sup>13</sup> obtained hypolipemia in cats after the administration of olive oil with as many as six subcutaneous injections of thyreotropic hormone. More than six injections, however, caused hyperlipemia.

Bing and Heckscher<sup>14</sup> obtained low values for the ether-soluble substances of the blood in patients with exophthalmic goiter. The response to 1 Gm of cream per kilogram of body weight was the same as in normal controls except that the increase of blood fat terminated in from three to four hours in the patients with thyroid disturbance while in the normal controls it continued five hours or more. As the symptoms decreased and after thyroidectomy, the fat and cholesterol content increased. These authors also found in later work<sup>15</sup> that the fat and cholesterol content of the blood in three myxedematous patients was increased and when thyreiodine was administered it decreased. Clinical hyperthyroidism produced by overdoses of thyreiodine caused the blood fat and cholesterol values to fall far below the normal concentration. Heckscher<sup>16</sup> observed high blood fat values in adult cretins. In young cretins the values were about normal, but the increase four or six hours after a fat meal was considerably greater than in normal subjects of the same age.

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Nicholls and Perlzweig<sup>17</sup> reported a decrease of fatty acids and cholesterol in the plasma of untreated patients with hyperthyroidism, with an increase after treatment with iodine and operation. Parhon and Ornstein<sup>18</sup> stated that intramuscular injections of thyroxin caused a decrease in the cholesterol and fatty acids in five patients.

Kugelman<sup>19</sup> determined the fat content of the blood during nineteen hours after a carbohydrate-free, fat-rich evening meal in healthy persons and found an increase during the night but a definite decrease by midday. In thyrotoxic patients there was an increase up to midday. Alpern, Tutkewitsch and Besuglow,<sup>20</sup> Leites<sup>21</sup> and Tsuda<sup>22</sup> found that subcutaneous injections of thyroxin in dogs decreased the alimentary blood lipid content after feeding of fat. Leites and Tsuda observed more marked results in male than in female dogs. Parhon and Ornstein<sup>2</sup> noted an increase in the fatty acids and cholesterol of the blood after thyroparathyroidectomy in eight of ten dogs.

Heckscher<sup>24</sup> removed the thyroid gland from a healthy horse and subsequently found an increase in the fat and cholesterol content of the blood. If fat was added to the diet the increase was greater in the thyroidectomized horse than in the normal animal. Nokazawa<sup>25</sup> reported that large doses of thyroid extract reduced the fat content of the whole blood of mice.

More observations have been made on the blood cholesterol in thyroid disease than on the fatty acids. Epstein and Lande,<sup>26</sup> C. J. and M. Parhon,<sup>27</sup> Mason, Hunt and Hurxthal<sup>28</sup> and Hurxthal<sup>29</sup> obtained diminished cholesterol values in patients with exophthalmic goiter. Improvement in the condition due to medical or surgical treatment resulted in a rise in the blood cholesterol to normal levels. These authors, as well as

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Luden,<sup>30</sup> Gardner and Gainsborough,<sup>31</sup> Laroche,<sup>32</sup> Hillmann<sup>33</sup> and Bronstein<sup>34</sup> found a marked increase in the blood cholesterol in patients with myxedema, when thyroid treatment was administered the content was reduced. Epstein and Lande<sup>26</sup> concluded that a definite inverse relationship exists between the cholesterol value and the basal metabolic rate. Castex and Schteingart<sup>35</sup> and Bonilla and Moya,<sup>36</sup> on the contrary, could find no relation between the basal metabolic rate and the blood cholesterol value. They concluded that any hypocholesteremia or hypercholesteremia observed in patients with thyroid disease depends not on these conditions but on concomitant causes. Denis,<sup>37</sup> Gechman<sup>38</sup> and Laroche<sup>32</sup> obtained low cholesterol values in extreme cases of hyperthyroidism, while in less serious cases they found normal values. On the other hand, Luden<sup>30</sup> stated that the blood cholesterol in thirty-five cases of exophthalmic goiter was within normal range, even when the basal metabolic rate was 100 per cent above normal. Gardner and Gainsborough<sup>31</sup> and Hinton<sup>39</sup> reported normal cholesterol values in their patients with hyperthyroidism. Hillmann<sup>33</sup> found the blood cholesterol values below normal in five patients with exophthalmic goiter and slightly above normal in six. Rosa and Furtado<sup>40</sup> obtained normal or slightly higher values in nine of eleven patients with hyperthyroidism. Wade<sup>41</sup> observed slightly increased values in thyrotoxic patients before operation. Rothschild and Jacobsohn<sup>42</sup> reported an increase of 20 per cent above the normal values for cholesterol in subjects with experimentally produced thyrotoxic conditions. Macciotta<sup>43</sup> recorded that thyroiodine increases the serum cholesterol in babies. Pighini and de Paoli<sup>44</sup> observed an increased blood cholesterol during the long administration

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of thyroid extract and concluded that cholesterol fixes and neutralizes the thyroid hormone in hyperthyroidism

M M and E Lévy<sup>45</sup> found that thyroxin reduced the cholesterol values to normal in patients with hypercholesteremia Christie, Lyall and Anderson<sup>46</sup> observed a great diminution of the blood cholesterol under thyroid therapy in a patient with xanthomatosis with a low basal metabolic rate and hypercholesteremia Duncan<sup>47</sup> gave thyroid treatment to twenty-two patients with mental disease and obtained a rapid lowering of the serum cholesterol, while Epstein<sup>48</sup> and Liu<sup>49</sup> reduced the hypercholesteremia in nephrosis with thyroid extract Turner<sup>50</sup> discovered that when thyroid was administered simultaneously with cholesterol it prevented the atheromatous changes usually produced by the administration of this lipid to rabbits Goldzieher and Hirschhorn<sup>51</sup> asserted that thyroid residue administered to animals at the same time that an emulsion of cholesterol is injected intraperitoneally prevents the normal storage of cholesterol in the Kupffer cells of the liver

Parhon and H and M Derevici,<sup>52</sup> Trifon<sup>53</sup> and Blinoff<sup>54</sup> demonstrated that dogs with hyperthyroidism had blood cholesterol values lower than those of normal dogs However, Clevers<sup>55</sup> observed an increase in the serum cholesterol in dogs with hyperthyroidism Leupold and Seisser<sup>56</sup> and Kusaka<sup>57</sup> found a decrease of the blood cholesterol in rabbits with hyperthyroidism Leupold<sup>58</sup> stated that small doses of thyreoidine decreased the cholesterol content of the blood in rabbits

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while large doses increased it Remond, Colombies and Bernardbeig,<sup>59</sup> Kunde,<sup>60</sup> Werner,<sup>61</sup> Onizawa,<sup>62</sup> Yoshimura,<sup>63</sup> Kunde, Green and Burns<sup>64</sup> and Westra and Kunde<sup>65</sup> noted in thyroidectomized rabbits high cholesterol values, which were reduced by the administration of thyroid. However, Turner and Khayat<sup>66</sup> claimed that thyroidectomy in itself does not cause a rise in the blood cholesterol of rabbits.

From the foregoing review of the literature the following facts are evident. First, little has been done on the problem of fat metabolism in hyperthyroidism, second, conflicting results have been obtained by different workers, some of which are probably due to the use of different methods and others to the use of a single injection of thyroid, with the tests made immediately or of several injections, with the tests made one or two days later, third, of the few investigators who studied the fat content of the blood in relation to thyroid disease, the majority observed hyperlipemia in hypothyroidism and hypolipemia in hyperthyroidism, fourth, the majority of investigators observed hypercholesteremia in hypothyroidism and a normal or diminished cholesterol content of the blood in hyperthyroidism, and fifth, there seems to be no difference in the results in different species of animals.

#### METHODS

These experiments were an attempt to determine the effect of hyperthyroidism on fat metabolism. Twenty-two adult dogs were used, four died of acute thyrotoxicosis, and the observations on three others were discontinued because of infections. Complete results were obtained for fifteen animals. Thyrotoxicosis was produced by feeding 10 Gm of desiccated thyroid daily with the food. Within a week after the feeding of thyroid was begun the dogs began to show loss of weight, great excitability and diarrhea.

Tests for fat tolerance were made on each dog every two or three weeks throughout the experiment until it died. From two to three tests were made before the animal was fed thyroid, these served as controls. The dogs were fed thyroid for different lengths of time, varying from two to three months according to the reaction to it. Then the feeding of thyroid was stopped for from six weeks to two months. This alternation was kept up until the dog died.

The following procedure was used in the fat tolerance tests. After the dog had been starved for four days, 15 cc of blood was withdrawn from a vein, 10 cc was placed in a centrifuge tube containing 4 drops of a saturated solution of sodium oxalate, and 5 cc was placed in another tube containing 2 drops of the oxalate.

59 Remond, A. Colombies, H., and Bernardbeig, J. *Compt rend Soc de biol* **91** 445, 1924.

60 Kunde, M. M. *Am J Physiol* **76** 225, 1926.

61 Werner, G. *Compt rend Soc de biol* **100** 928, 1929.

62 Onizawa, J. *J Biochem* **10** 425, 1929.

63 Yoshimura, O. *J Chosen M A* **21** 1079, 1931.

64 Kunde, M. M., Green, M. F., and Burns, G. *Am J Physiol* **99** 469, 1932.

65 Westra, J. J., and Kunde, M. M. *Am J Physiol* **103** 1, 1933.

66 Turner, K. B., and Khayat, G. B. *J Exper Med* **58** 127, 1933.

solution to be used for other chemical tests. The dog was fed 2 cc of olive oil per pound (0.45 Kg) of body weight. At one, three, five and seven hour intervals thereafter 15 cc of blood was withdrawn. The total fatty acid and cholesterol content of the plasma in each of the five samples was determined by Bloor's<sup>67</sup> oxidation method.

In order to determine the amount of fat lost in the stools, the fat in the feces of four dogs was determined at the same time that the fat tolerance tests were made. Two specimens were obtained, one during the starvation period before olive oil was given, the other was the first specimen after the administration of the olive oil. The total fat was estimated by Saxon's<sup>68</sup> method, and duplicate tests were made on each sample.

All the glassware used in the tests was free from fat. In all, there were 2,928 determinations, 1,400 titrations of fatty acids, 238 of which were controls, 1,400 colorimetric determinations of cholesterol, 238 of which were standards, and 128 determinations of fat in the feces.

#### RESULTS OF EXPERIMENTS

*Normal Initial Blood Lipoid Values*—The twenty-two animals showed a marked individual difference in the fat content of the blood at the beginning of the experiment. There seemed to be no similarity in the initial value for blood fat, that is, in the sample taken just prior to feeding the oil, for any one sex or species. The average normal initial value for fatty acids was 313.3 mg per hundred cubic centimeters, with a range from the minimum of 189 mg to a maximum of 654 mg. In any one dog the maximum difference among the several values was 157 mg, and the minimum difference, zero, with an average of 62 mg. The average normal initial cholesterol value was 128.9 mg per hundred cubic centimeters, with a range from a minimum of 76 mg to a maximum of 202 mg. In any one dog the maximum difference was 51 mg, and the minimum, zero, with an average of 17.6 mg.

However, because of death from infections or acute thyrotoxicosis it was possible to obtain complete results for only fifteen dogs after the feeding of desiccated thyroid. The average normal initial blood fat content of the fifteen dogs varied only slightly from that of the twenty-two dogs, the initial fatty acid content averaging 315.2 mg per hundred cubic centimeters and the cholesterol value averaging 126 mg.

*Initial Blood Lipoid Values During First Period of Feeding of Thyroid*—After two or three weeks of feeding of thyroid the average initial fatty acid content for the fifteen dogs was 300 mg per hundred cubic centimeters. This was 15.2 mg lower than the normal average for the same dogs. The animals can be divided into three groups. The first consists of six dogs in which the initial fatty acid content was from 26 to 176 mg lower than the lowest corresponding normal value.

<sup>67</sup> Bloor, W. R. J. Biol. Chem. **77** 53, 1928.

<sup>68</sup> Saxon, G. J. J. Biol. Chem. **17** 99, 1914.

The average for these dogs after feeding of thyroid was 2387 mg, which was 953 mg lower than the average (334 mg) of the lowest normal values for these six dogs. The second group consisted of one dog in which the initial fatty acid content was lower than its corresponding high normal value. The amount after feeding of thyroid was 396 mg, which was 44 mg lower than the highest normal value. The third group consisted of eight dogs in which the initial fatty acid value was from 5 to 93 mg higher than the highest corresponding normal value. The average after feeding of thyroid was 3339 mg, which was 295 mg higher than the average (3044 mg) of the highest normal values for the eight dogs.

The average initial cholesterol value after feeding of thyroid was 1153 mg per hundred cubic centimeters which was 157 mg lower than the normal average value. The dogs can again be divided into three groups. The first consists of eight dogs in which the initial cholesterol value was from 1 to 74 mg lower than the lowest corresponding normal value in the group. The average for these dogs after feeding of thyroid was 104 mg, which was 27 mg lower than the average (131 mg) of the lowest normal values for the eight dogs. The second group consisted of three dogs in which the initial cholesterol value was lower than the corresponding high normal value. The average after feeding of thyroid was 121 mg, which was 28 mg lower than the average (149 mg) of the highest normal values for the three dogs. The third group consisted of four dogs in which the initial cholesterol value was from 2 to 38 mg higher than the highest corresponding normal value. The average after feeding of thyroid was 1325 mg, which was 165 mg higher than the average (116 mg) for the highest normal value for the four dogs.

As feeding of thyroid continued the initial fatty acid content in all but four dogs increased, reaching the maximum from six to nine weeks after the feeding of thyroid was begun. The maximum increase was 372 mg at eight weeks in dog 8. The minimum increase was 7 mg at five weeks. In three dogs in which there was a decrease the first initial blood fat value for each dog after feeding of thyroid was higher than the normal value for that dog. This increase made the average initial fatty acid content for all the tests on the fifteen dogs during the entire period of feeding of thyroid 109 mg higher than the normal average.

As feeding of thyroid continued the initial cholesterol value in all the dogs increased, the range being from 2 to 87 mg. However, this increase was not as great in comparison to the increase in fatty acids, as shown by the average cholesterol value for the fifteen dogs, which was exactly the same as the average for the normal dogs.

*Initial Blood Lipoid Values After First Period of Feeding of Thyroid*—Eight dogs survived a period of feeding of thyroid of from two

to fourteen weeks, then feeding of thyroid was discontinued for a period of from three to eight weeks. During the rest period the blood fat showed a great increase. The initial fatty acid value increased in the first test in seven of the eight dogs, the range of increase being from 6 to 258 mg, with an average of 119.7 mg. The one dog (dog 12) that did not show an increase had been fed thyroid for only two weeks and probably had not become as thyrotoxic as the others, which had been fed thyroid for at least six weeks. Those which had been fed thyroid for from nine to eleven weeks showed the greatest increase. In only two dogs (except dog 12) was the initial fatty acid value after discontinuation of feeding of thyroid lower than the highest value during feeding of thyroid. The average initial fatty acid value was 446.3 mg, which was 120.2 mg higher than the average during feeding of thyroid and 131.1 mg higher than the normal average before feeding of thyroid.

The cholesterol was greatly increased in all the dogs throughout this period. The increase in the initial cholesterol content varied from 10 to 175 mg, and at no time was the cholesterol value as low as the highest value during the previous period. The average initial cholesterol value was 206.9 mg, which was 80.9 mg higher than the average value during feeding of thyroid and the normal average before feeding of thyroid.

*Initial Blood Lipoid Values During Second Period of Feeding of Thyroid*—Six dogs were again fed thyroid after the rest period. All these showed a decrease of from 16 to 90 mg in the initial fatty acids determined by the first test, which was a much greater decrease than in the first period of feeding of thyroid. The average for the first tests was 332.5 mg, which was 93.5 mg lower than the average for the rest period for these six dogs. All the initial fatty acid values except one were lower than the lowest value in the preceding period. The average was 366.8 mg, which was 79.5 mg lower than the average for the previous period.

The initial cholesterol also showed a decrease, the values for the first test ranging from 7 to 136 mg lower than the values in the last test of the previous period. The cholesterol did not show as great a decrease throughout the second period of feeding of thyroid as did the fatty acids. The average initial cholesterol value was 165.9 mg, which was 41 mg lower than the average of the previous period.

*Normal Curve for Blood Lipoids After Feeding of Olive Oil*—As in the initial blood fat values, there seemed to be no regularity in the degree of hyperlipemia produced by feeding of olive oil either in the individual dog or in the sex or species. Although there was no great difference in the initial fat and cholesterol values in the several tests on the same dog under normal conditions, there was a great difference



in the degree of hyperlipemia produced after feeding of olive oil and in the hour in which the highest values were obtained. The lowest percentage of increase over the initial fat value was 1.7 per cent, and the highest, 102.63 per cent. The average increase in values for all the tests under normal conditions was 52.06 per cent. The greatest individual difference was 92.02 per cent. The height of the curve was reached at five hours in the largest number of tests on the twenty-two dogs, as demonstrated in table 2. However, in table 4 it is

TABLE 1—*Average Curve for Blood Lipoids for Forty-Three Tests on Twenty-Two Normal Dogs*

Olive Oil	Fatty Acids, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Total, Mg per 100 Cc
Before	313.3	128.9	442.2
1 hour after	357.6	127.1	484.7
3 hours after	453.0	124.0	577.0
5 hours after	465.6	127.9	593.5
7 hours after	464.6	128.1	592.7

TABLE 2—*Height of Curve for Blood Lipoids for Forty-Three Tests on Twenty-Two Normal Dogs*

Peak	Number of Tests	Percentage of Tests
1 hour	2	4.65
3 hours	12	27.91
5 hours	17	39.53
7 hours	12	27.91

TABLE 3—*Average Curve for Blood Lipoids for Thirty-One Tests on Fifteen Normal Dogs*

Olive Oil	Fatty Acids, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Total, Mg per 100 Cc
Before	315.2	126.0	441.2
1 hour after	358.8	125.0	483.8
3 hours after	450.0	120.6	570.6
5 hours after	428.0	121.8	549.8
7 hours after	430.1	123.0	553.1

shown that as many values reached the peak at seven hours as at five hours in the fifteen dogs that were later fed desiccated thyroid.

The cholesterol content did not increase with the fatty acid content but remained practically the same throughout the seven hours, as shown in the average figures for forty-three fat tolerance tests made on twenty-two normal dogs (table 1). In tables 3 and 4 are shown the average results of thirty-one fat tolerance tests and the height of the curve for blood lipoids for the fifteen dogs which were later fed desiccated thyroid.

*Curve for Blood Lipoids After Feeding of Olive Oil During First Period of Feeding of Thyroid*—There was a greater increase in the curve for blood lipoids after feeding olive oil during the period of feeding of thyroid than under normal conditions. The average percentage of increase in the first test was 59.3 per cent, which was higher than the average for the period. The greatest increase was in a female dog. The lowest percentage of increase over the initial value for fatty acid plus cholesterol was 2.55 per cent, and the highest 170.15 per cent. The greatest individual difference was 166 per cent. The average increase for all the values during feeding of thyroid was 53.38 per cent. This is confirmed in table 5, which shows that the average increase after feeding of thyroid was 37.22 per cent (from 452.1 to

TABLE 4—*Height of Curve for Blood Lipoids for Twenty-One Tests on Fifteen Normal Dogs*

Peak	Number of Tests	Percentage of Tests
1 hour	2	6.45
3 hours	9	29.03
5 hours	10	32.26
7 hours	10	32.26

TABLE 5—*Average Curve for Blood Lipoids for Fifteen Dogs During First Period of Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Total, Mg per 100 Cc
Before	326.1	126.0	452.1
1 hour after	344.4	121.3	465.7
3 hours after	452.2	127.1	579.3
5 hours after	494.4	126.0	620.4
7 hours after	470.9	127.1	598.0

620.4 mg), while it was only 29.32 per cent in table 3 (from 441.2 to 570.6 mg), showing the average for fifteen normal dogs, and 34.21 per cent in table 1 (from 442.2 to 593.5 mg), showing the normal average for twenty-two dogs. There was a general shift of the height of the curve for blood lipoids to the fifth and seventh hours, with a greater percentage of increase in this period than in either of the normal groups of fifteen and twenty-two dogs. This is demonstrated by comparing tables 2, 4 and 6. For the twenty-two normal dogs, the curves for blood lipoids had their peaks at five or seven hours in 67.44 per cent of the tests (table 2), for the fifteen normal dogs, in 64.52 per cent (table 4). For the fifteen dogs fed thyroid the curves had their peaks at five and seven hours in 81.2 per cent of the tests (table 6). The average cholesterol curve remained practically the same as the normal cholesterol curve.

*Curve for Blood Lipoids After Feeding of Olive Oil After First Period of Feeding of Thyroid (First Rest Period)*—During the rest period after feeding of thyroid had been discontinued, although the initial values for fatty acids plus cholesterol were greatly increased, the degree of hyperlipemia after the feeding of olive oil was decreased. The lowest percentage of increase over the initial values was 3.83 per cent, and the highest 43.57 per cent, except for a 53.73 per cent increase in dog 12, which had been fed thyroid for only two weeks and did not show an increase in the initial blood fat value. The greatest individual difference was 28.89 per cent. The average increase for all the values was 23.52 per cent. The increase in the curve for blood lipoids in table 7 (from 653.2 to 775.8 mg) was only 18.76 per cent. The

TABLE 6—*Height of Curve for Blood Lipoids for Fifteen Dogs During First Period of Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	0	0
3 hours	8	18.8
5 hours	18	43.7
7 hours	15	37.5

TABLE 7—*Average Curve for Blood Lipoids for Eight Dogs After Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Total, Mg per 100 Cc
Before	446.3	206.9	653.2
1 hour after	482.6	197.9	680.5
3 hours after	522.4	198.9	721.3
5 hours after	579.3	196.5	775.8
7 hours after	527.2	189.7	716.9

height of the peak appeared in a greater percentage at five hours (in 62.5 per cent of the tests) and in a much lower percentage at seven hours (in 25 per cent of the tests), as seen in table 8, than in either the normal dogs or those with hyperthyroidism. Although the cholesterol content was greatly increased before feeding of olive oil, it continued to be high throughout the seven hours, but showed a slight decrease—from 206.9 to 189.7 mg (table 7).

*Curve for Blood Lipoids After Feeding of Olive Oil During Second Period of Feeding of Thyroid*—During the second period of feeding of thyroid the increase in the curve for blood lipoids was not as great as during the first period. The lowest percentage of increase was 11.88 per cent, and the highest 89.87 per cent, both of which were in the same dog. Corresponding values in the first period were 2.55 and 170.15 per cent. The average increase for the separate tests was 42.6

per cent (contrasted with 53.33 per cent) The increase in the average curve for blood lipoids in table 9 (from 532.7 to 714.1 mg) was 34.21 per cent The height of the curve for blood lipoids again occurred most frequently at five hours, but there was a higher percentage at three hours (31.3 per cent) than at seven hours (6.2 per cent), as shown in table 10 This is the opposite of the findings shown in table 8 for the rest period The cholesterol content remained practically the same

TABLE 8—*Height of Curve for Blood Lipoids for Eight Dogs After Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	2	12.5
3 hours	0	0
5 hours	10	62.5
7 hours	4	25.0

TABLE 9—*Average Curve for Blood Lipoids for Six Dogs During Second Period of Feeding of Thyroid*

Olive Oil	Fatty Acids, Mg per 100 Cc	Cholesterol, Mg per 100 Cc	Total, Mg per 100 Cc
Before	366.8	165.9	532.7
1 hour after	396.5	159.9	556.4
3 hours after	546.5	159.3	705.8
5 hours after	554.1	160.0	714.1
7 hours after	452.2	157.1	609.3

TABLE 10—*Height of Curve for Blood Lipoid for Six Dogs During Second Period of Feeding of Thyroid*

Peak	Number of Tests	Percentage of Tests
1 hour	0	0
3 hours	5	31.3
5 hours	10	62.5
7 hours	1	6.2

as the initial amount throughout the seven hours, that is, lower than that in the previous period

*Fat Content of Feces*—The normal percentage of increase in the fat content of the feces after feeding olive oil was high In eight tests on the four dogs in which complete results were obtained the average increase was 314.91 per cent over the fat content before olive oil was given In only one test was the increase less than 100 per cent During the first period of feeding of thyroid there was a great decrease in the percentage of increase, especially in the first test after

the beginning of the feeding. The average increase during feeding of thyroid was 187.22 per cent. For only one dog (dog 27) were any of the values higher than those obtained under normal conditions. If the two extremely high values for this animal were left out of the calculation for the period of feeding of thyroid the average increase would be only 90.13 per cent. In the three dogs for which feeding of thyroid was discontinued the first values showed a percentage of increase of 194, while the first values during feeding of thyroid showed a percentage of increase of 88. The average increase during the rest period was 152.32 per cent. The feces of only one dog were examined further, during the second period of feeding of thyroid there was an average increase of 43.06 per cent for three tests.

#### SUMMARY OF RESULTS

There appears to be no regularity in the initial fatty acid or cholesterol content of the blood in different dogs of either sex or of any species.

The type of curve for blood lipoids varied in the individual dog at different times and in the two sexes and the various species.

The initial fatty acid value determined by the first test after feeding of thyroid was slightly lower than the normal value for the individual dogs.

If feeding of thyroid was continued for from six to nine weeks the initial fatty acid content increased.

The cholesterol value remained practically the same as the normal value throughout the period of feeding of thyroid.

The percentage of increase in the curve for blood lipoids after feeding olive oil was greater during the period of feeding of thyroid than in the normal curve.

During the rest period after feeding of thyroid the initial fatty acids and the cholesterol increased greatly.

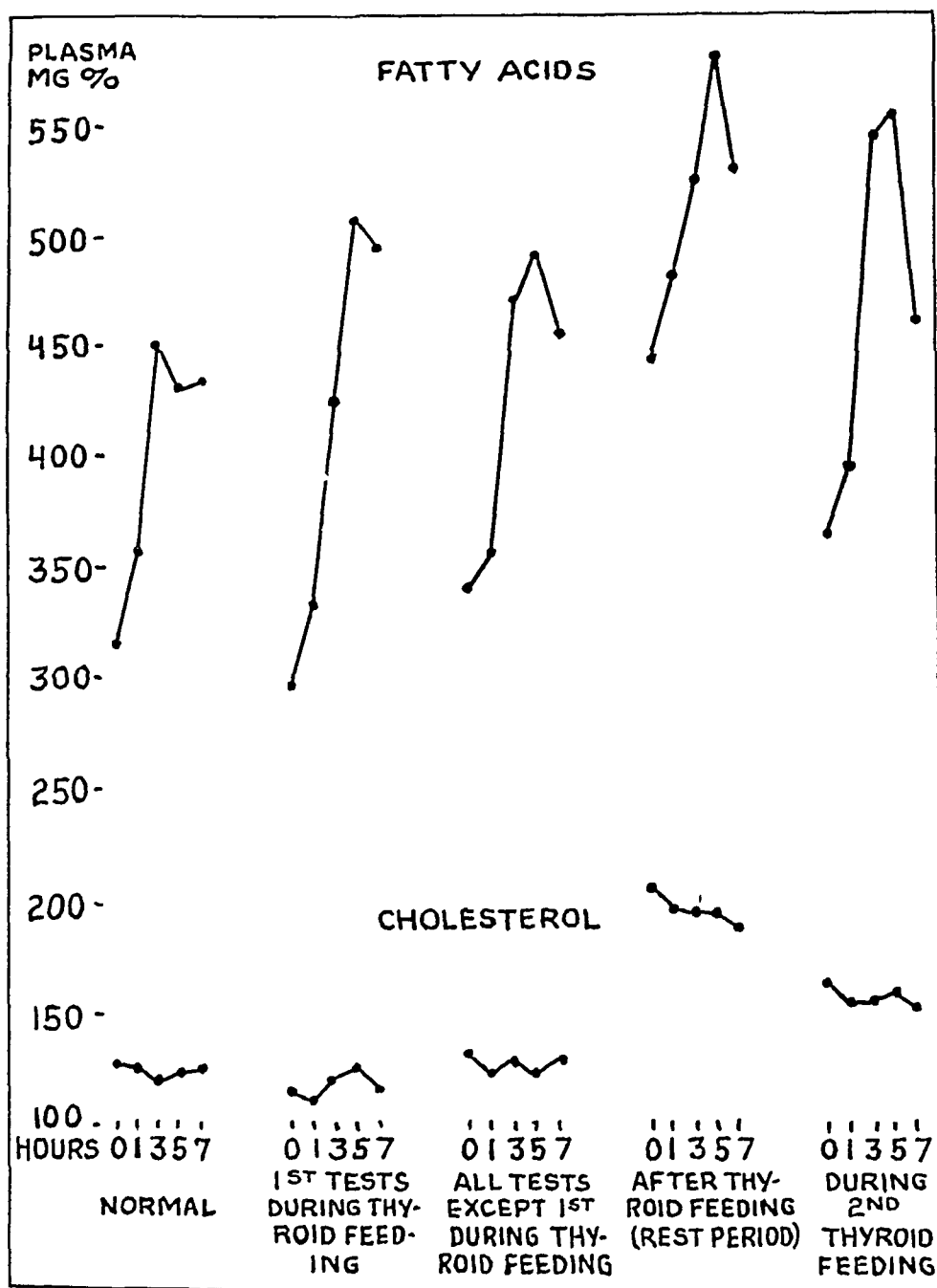
The percentage of increase in the curve for blood lipoids during the rest period was lower than that in the normal period.

During the second period of feeding of thyroid the initial fatty acid and cholesterol values showed a much greater decrease than during the first period of feeding of thyroid.

The percentage of increase in the curve for blood lipoids was greater during the second period of feeding of thyroid than in the rest period, but not as great as during the first period of feeding of thyroid.

During the periods of feeding of thyroid the percentage of increase in the fat content of the feces after feeding olive oil was much less than the normal percentage of increase.

In a preliminary report on seven dogs of this series, Simonds and I<sup>69</sup> concluded that the total lipid content of the blood plasma is lowered in experimental hyperthyroidism. A more careful analysis



Average curves for blood lipids in tests for fat tolerance in hyperthyroidism

of a larger number of determinations on fifteen dogs compelled me to modify that opinion to the extent indicated in the summary

<sup>69</sup> Simonds, J. P., and Hepler, O. E. Fat Tolerance in Experimental Hyperthyroidism, *J. A. M. A.* **98** 283 (Jan 23) 1932

The foregoing results are demonstrated in the chart, which shows the average fatty acid and cholesterol curves for fifteen dogs during the various periods of these experiments

#### COMMENT

After the ingestion of fat there is a continuous absorption of this substance from the intestines into the blood stream and a concomitant continuous passage of fat from the blood into the tissues. The curve for blood lipoids determined by the fat tolerance test represents the difference in the rates of these two processes, that is, the absorption of fat and its utilization or storage. A careful study of the literature failed to reveal any evidence that increased digestion of fat or more rapid absorption of it through the intestinal mucosa can be the cause of the increased blood fat in hyperthyroidism.

Two possible explanations of the hyperlipemia observed in my thyrotoxic dogs present themselves. First, feeding of thyroid has a direct action on the cells of the tissues. That this effect is progressive was demonstrated by Robles<sup>70</sup>. After feeding mice dried thyroid daily he found that tissue respiration was not increased in five days, was slightly increased in ten days and was increased in fifteen days from 20 to 30 per cent. The initial values for blood fat in my dogs were normal or slightly lower than normal during the period of from seventeen to thirty days after the beginning of feeding of thyroid. At this stage of thyrotoxicosis the cells were still capable of utilizing fat, although the slight decrease in the blood fat does not seem comparable to the increased consumption of oxygen of the cells. However, the breakdown of the reserve fat still available would normally cause an increase in the amount of blood fat and might explain the fact that the observed decrease associated with the increasing metabolism was not greater than it was found to be. As feeding of thyroid was continued the increasing toxic effect on the cells decreased their ability to utilize and store fat and thus increased the amount of fat in the blood. This explanation is not satisfactory, because seriously injured cells could hardly be expected to maintain the greatly increased metabolism in hyperthyroidism.

A second explanation may be that as the entire metabolism in hyperthyroidism is established at a higher level than normal so also is the sugar and fat content of the blood established and maintained at a higher level in order to sustain adequately the increased metabolism. Liebermeister<sup>71</sup> in 1875 expressed the view that in fever the

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70 Robles, E. *Frankfurt Ztschr. f. Path.* **41** 193, 1931.

71 Liebermeister, C. *Handbuch der Pathologie und Therapie des Fiebers*, Leipzig, F. C. W. Vogel, 1875, p. 359.

heat regulating mechanism is adjusted to a higher temperature level. The metabolism in hyperthyroidism is comparable to that in fever in that there are in both an increase in the blood sugar, a decrease in the glycogen of the liver and an increase in the general metabolism. Raab,<sup>72</sup> in 1929, described an increase in the blood fat in experimental fever in dogs but reported<sup>73</sup> in 1933 a decreased curve for blood lipoids after feeding olive oil to patients with fever.

In order to maintain the higher level of metabolism in hyperthyroidism the body must keep a greater amount of fuel in the blood for rapid utilization. While the animal is reaching the height of thyrotoxicosis the blood fat may be normal or slightly decreased because its necessary adjustment to a new and higher level does not keep pace with the metabolism. As the metabolism becomes established at a higher level, an increased amount of fat and sugar must be maintained in the blood in order to sustain the increased metabolism and to meet any emergency. This may be a protective mechanism. Hyperglycemia has been frequently observed in hyperthyroidism.

After feeding of thyroid is discontinued the stimulus of the increased metabolism is withdrawn. The thyroid glands of animals dying at the height of experimental thyrotoxicosis were found to be markedly atrophic. Hence in this condition the natural stimulus to metabolism is lacking, and a state of hypothyroidism exists. The decreased utilization of fat due to the decreased metabolism in hypothyroidism accounts for the great increase of the blood fat after the removal of the stimulus of feeding of thyroid. The body does not adjust itself so rapidly to this change. But after from six to eight weeks the blood fat decreased, showing that by that time either the body had adapted itself to a lower level of metabolism or the thyroid had again assumed its normal function.

The decrease in the initial fat and cholesterol values and in the blood lipid content after feeding olive oil was more marked during the second period of feeding of thyroid than during the first. In explanation of this it is suggested that because of the increased metabolism after a period in which the metabolism was less than normal there were a greater burning up of fat by the cells and a greater storage of fat. Abelin and Vuille<sup>74</sup> reported that animals become resistant to a second administration of thyroid extract after a two months' rest, as indicated by the ability of the liver to store glycogen. Oberdisse<sup>75</sup> confirmed this by finding that there was not as great an

72 Raab, W. *Wien Arch f inn Med* **18** 387, 1929.

73 Raab, W. *Ztschr f d ges exper Med* **89** 616, 1933.

74 Abelin, I., and Vuille, R. *Endokrinologie* **2** 248, 1928.

75 Oberdisse, K. *Arch f exper Path u Pharmakol* **162** 150, 1931.



increase in the metabolic rate during the second period of feeding of thyroid. However, in my dogs, as the second period of feeding of thyroid continued the blood fat gradually increased, showing that the body was again adjusting itself to a higher level of metabolism.

#### CONCLUSIONS

1 Feeding of thyroid slightly decreased the initial blood fat during the first month, that is, while the height of hyperthyroidism was being reached.

2 Continued feeding of thyroid was accompanied by an increase in the initial blood fat above the normal value.

3 During the first period of feeding of thyroid there was a decrease in the tolerance of the animal for fat, as demonstrated by the increased curve for blood lipoids.

4 The cholesterol values remained within normal limits during the period of feeding of thyroid.

5 During the rest period after the first period of feeding of thyroid, when the animal was in a state of hypothyroidism, the fat and cholesterol values increased.

6 The blood fat and cholesterol decreased during the second period of feeding of thyroid, possibly due in part to a resistance of the animal to a second administration of thyroid.

7 Two explanations for these results are suggested: first, that the thyroid extract injures by its toxic effect the tissue cells, rendering them incapable of maintaining their normal capacity for storing or utilizing fat, and, second, that in hyperthyroidism the metabolism of the body is established at a higher level and that the fuel constituents of the blood—fat and sugar—likewise must be established and maintained at a higher level in order to sustain this increased metabolism. The second explanation is the more satisfactory.

## DISSEMINATION OF AMEBIASIS

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The methods of infection by *Endamoeba histolytica* are more easily followed if one bears in mind the life cycle of the parasite. In this, two phases are recognized—that of the trophozoites or free living forms, capable of life only within the human host, and that of the cysts which survive both within and outside the human host. The trophozoites are found in the wall of the large intestine, where in different conditions they cause varying degrees of ulceration. If during this process they invade the tributaries of the portal vein they are carried to the liver, where they may cause hepatitis or abscess. Less commonly, abscess of the lung, of the brain or of other organs may occur. If the trophozoites are passed by rectum in a dysenteric stool they die rapidly in water or on exposure to air, and if conceivably they could be ingested by another person they would be killed by the gastric juice, therefore it should be realized that the disease-causing phase of the parasite is not the one by which infection is conveyed from man to man.

Should conditions in the colon become unsuitable for the trophozoites they tend to become encysted. They multiply so rapidly that they do not achieve their maximum size and they no longer cytolyze tissue or phagocytose debris and red blood cells. The small precystic parasites thus formed become less active than the parent cell and are subsequently motionless. Finally they secrete a transparent substance which forms an enveloping and highly resistant cyst wall. Persons who pass such cysts in formed or semiformed stools are called "carriers." The carrier may never be aware of any symptoms of infection and may be discovered to be a carrier only on routine examination of his stool. On the other hand, he may give a history of dysentery, or he may be a carrier during intervals between attacks of dysentery.

When passed by rectum the parasites within the cysts retain their vitality for a considerable time provided there is a minimum of moisture. They die rapidly on drying or on exposure to excessive heat. The gastric secretions do not affect them, therefore on entering a new host they pass through the stomach unchanged. In the small intestine the wall of the cyst is digested and the enclosed parasites are liberated.

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From the Department of Medicine, Presbyterian Hospital, Columbia University

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They do not invade the mucosa of the small intestine but are carried through the ileocecal valve to the cecum. Following rapid multiplication they become trophozoites in the large intestine. By means of a powerful secretion they cytolyze the cells of the mucosa and thus make their way to the submucosa and the deeper tissues.

If feces containing cysts are deposited on the ground or in open privies the cysts may be ingested by flies which are capable of depositing them unchanged on food. During rain, washings from feces may carry cysts to streams or wells, in which case infection may occur from drinking water. The number of cysts in the droppings of a fly is not large. Similarly, in water contaminated as described the cysts would be widely distributed and would not reach any one person in large numbers. The fact that amebiasis has generally been considered an endemic rather than an epidemic infection may be attributable to these factors. Furthermore, the fact that many persons become carriers without being conscious of symptoms and that in many clinical cases the onset of symptoms is insidious suggest that the original infection of parasites was small, that in the human host there is a tendency to the development of immunity against the parasite and that only when the resistance of the host is lowered do the parasites multiply with sufficient rapidity to produce the graver manifestations of amebiasis.

Observations have shown that there is a higher incidence of amebiasis among persons handling food than among others. This is especially the case when sanitary conditions are primitive, as in rural districts, in the poorer sections of many towns and in armies maintained under field conditions. The reason for this is probably related to the bionomics of the house-fly and other members of the muscid family which do not bite, such as the bluebottle, the greenbottle and flesh-flies which feed on both feces and food. As is well known, these flies congregate in their largest numbers in and about eating places. In adjacent privies or from excreta on the ground they may ingest cysts of *E. histolytica*, some of which they pass on food. As this is being repeated constantly, the food of the permanently employed is more likely to be infected than is that of the transient guest. During the recent epidemic in Chicago no cases of amebiasis occurred among the guests in several hotels with a high incidence of carriers on the staff. On the other hand, in two other hotels having the same or lower incidence of carriers, amebic dysentery among the guests assumed epidemic dimensions. A study of 68 carriers was made to see whether cysts might be transmitted by the fingers or the finger-nails, but no parasites were found by either direct microscopic or cultural methods. Moreover, Kaplan has shown that in such quantities of feces as might conceivably adhere to the hand the cysts die within from three to five minutes. These facts suggest that the menace of the person who handles

food is in relation to the accessibility of his excrement to flies and other disseminating sources rather than to any contamination of his hands, except in very rare instances. Here again it is clear that the number of cysts that might possibly be conveyed by the hands must be very small, and by such a method of transmission one might expect only an endemic spread of infection with only mild or subacute symptoms exhibited in many of the cases.

Small foci of amebiasis are not infrequently found in the United States, and Craig (1916) in the study of an outbreak among the troops at El Paso, Texas, observed 118 cases of clinical amebiasis in which the method of infection was definitely attributable to flies. There is, however, no authentic record of an epidemic of amebiasis of the magnitude of that in Chicago in 1933, in which 1,122 cases with 51 deaths have been reported. The outbreak was found to have originated mainly in two adjacent hotels.

At the Presbyterian Hospital, from 4 to 8 cases of amebiasis are studied each month. Fifty per cent of the patients are carriers without apparent symptoms, the remaining half have clinical amebiasis. Among the latter, the symptoms vary from simple diarrhea with a loss of weight to an occasional acute attack of amebic dysentery, but the so-called fulminating type of amebic dysentery commonly seen in the tropics is rarely observed. In September 1933 a patient with a severe case of amebic dysentery was admitted, and since that time 20 cases have been studied in the hospital, all the patients having visited Chicago in 1933. In addition, I have studied other cases in Chicago and have seen the autopsy material in 5 fatal cases. Furthermore, through the courtesy of the president of the Chicago Board of Health, I have been able to study the clinical histories in the replies to questionnaires from many other patients. From the various sources some suggestive facts have emerged.

Many persons were exposed to infection for only a few hours. In a large percentage the period between the exposure and the onset of symptoms was very short, averaging from ten to fifteen days. In the majority of victims the onset of acute dysentery was sudden, without previous discomfort or warning. The symptoms were generally more severe than those seen in general practice in this country, and the course of the disease was rapid. The frequency of tenesmus indicated that the rectum was involved in most cases. Complications in the liver, especially abscess, were common and occurred shortly after exposure to the infection. A study of the autopsy material confirmed the clinical histories and observations. In most cases the greater part of the mucous membrane of the colon was destroyed. Typical amebic ulcers were invariably found in the rectum at autopsy and on proctoscopic examination during life. In the 5 autopsies mentioned the liver showed multiple

abscesses, and in 1 case an abscess was also found in the lung. The foregoing observations were made on severe or fulminating types of amebic dysentery, which were in marked contrast to the subacute picture usually seen in this country.

The facts described suggested that in many cases the method of infection could not possibly be explained by the hitherto recognized methods. In Chicago, flies are a minor problem, and there are neither wells nor streams from which drinking water is supplied. Considering all the facts, it seemed reasonable to assume that infection in this epidemic was due to a massive contamination with cysts of *E. histolytica* of the drinking water of the two hotels in question. This seemed more likely since one hotel derives its water from the main which supplies the other. On such a supposition it is conceivable that the patients ingested large numbers of cysts on one occasion and probably in many instances within a short space of time, before any immunity could be developed in the host. Such a possibility would explain the very rapid onset of symptoms.

In November 1933 a survey by sanitary engineers of the Chicago Board of Health was made of the plumbing of the hotels concerned, and three potential disease hazards were discovered. When many of the toilets were flushed at the same time, as would occur when a hotel is full to capacity with guests, back siphonage from toilets to the water mains was observed. In June 1933, during local storms, water from the street penetrated to the basement of one of the hotels, resulting in the mixture of floor water and feces from an open sewer which submerged the ice plant and other equipment of the hotel. Subsequently cross-connections were found between the sewage pipes and the mains for drinking water. While it has not been definitely decided which of these hazards was particularly responsible for the outbreak, it seems probable that on the evidence available the cross-connections, notoriously the cause of recent epidemics of bacterial disease, will be found to be the responsible agent.

Since there are carriers in all parts of the United States and since definite foci of infection have been reported in some localities, it is possible that in many large cities where hotels possess antiquated plumbing such outbreaks as occurred in Chicago will again occur under conditions of congestion.

The relatively large number of cases of amebiasis encountered each month during routine practice at the Presbyterian Hospital is not considered alarming. The patients come from all over this continent and others and their cases represent mainly sporadic instances of infection, but when even a small "group" of cases presents itself from one locality or when more than one member of a family is found to be infected, the most stringent inquiry should be instituted with a view to preventing a further spread of the infection.

# BLOOD

## A REVIEW OF THE RECENT LITERATURE

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To those who have been closely identified with the field of diseases of the blood it is unnecessary to state that during the past decade there has been at least as much progress in the field of hematology as in any other aspect of internal medicine. Important contributions from both a clinical and a scientific standpoint have been made in recent years from almost every country in the world. As a result, a voluminous literature bearing on the subject has accumulated which makes a complete review impossible. We have attempted, therefore, to select only those articles which have the most important bearing on the recent advances in the subject. Doubtless some valuable papers have been unintentionally omitted, and for these omissions we extend our apologies.

Although the primary purpose of this review is to consider the work of the past year in hematology, a number of fundamental articles published prior to this time have been included for the sake of completeness.

## PERNICIOUS ANEMIA

### ETIOLOGY

Any discussion of the etiology of pernicious anemia would be incomplete if it did not include a résumé of the fundamental work of Castle and his associates which was published in the *American Journal of Medical Sciences* during the years 1929 to 1931<sup>1</sup>. In a series of care-

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1 (a) Castle, W B. Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am J M Sc* **178** 748, 1929. (b) Castle,

(Footnote continued on next page)

fully performed experiments it was demonstrated that in patients with pernicious anemia there is an inability of the gastric mucosa to secrete an unidentified substance (the intrinsic factor) which interacts with some article of diet to form a material which controls the maturation of the red blood cells in the bone marrow. It was demonstrated that the underlying cause of true addisonian pernicious anemia is a defect in the gastric secretion. The exact nature of the intrinsic factor has not been determined. It is not one of the known components of the gastric juice such as hydrochloric acid, rennin or pepsin, but it is an organic substance; it is thermolabile, and there is some evidence which indicates that it is possibly an enzyme or an enzyme-like substance.

Strauss and Castle<sup>2</sup> have stated that the extrinsic factor may be defined as a substance closely related to vitamin B<sub>2</sub> if it is not vitamin B<sub>2</sub>. They gave a patient with true addisonian pernicious anemia 12 Gm daily of an autolyzed yeast preparation for ten days without effect. When the same amount of this preparation was administered daily with 150 cc of normal human gastric juice a characteristic reticulocytic response and an increase in the total red blood cell count resulted. Other observers<sup>3</sup> using the whites of hens' eggs as a source of vitamin B<sub>2</sub> were unable to influence the regeneration of red blood cells when this substance was given alone or after incubation with gastric juice. Lassen and Lassen<sup>4</sup> gave various yeast preparations alone and after incubation with gastric juice and concluded that the preparations are without any effect or possibly contain minimal amounts of the anti-

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W B, and Townsend W C. Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Gastric Juice. *ibid* **178** 764, 1929. (c) Castle, W B, Townsend, Wilmot C, and Heath, Clarke, W. Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid* **180** 305, 1930. (d) Castle, W B, Heath, Clarke, W, and Strauss, M B. Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Role of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *ibid* **182** 741, 1931.

2 Strauss, M B, and Castle, W B. The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, Activation of Yeast Derivatives with Normal Human Gastric Juice, *New England J Med* **207** 55, 1932.

3 Wills L and Naish, A. A Case of Pernicious Anemia Treated with Vitamin B<sub>2</sub> from Egg White, *Lancet* **2** 1286, 1933.

4 Lassen, H C, and Lassen, H K. Yeast or Vitamin B<sub>2</sub> as "Extrinsic Factor" in Treatment of Pernicious Anemia, *Am J M Sc* **188** 461, 1934.

anemia factor. They concluded that the extrinsic factor is not identical with any fraction of the vitamin B complex. It is stated, however, that some kinds of commercial yeast or yeast preparations contain a certain amount of antianemia principle. Wills concluded<sup>5</sup> that one preparation, which is an autolyzed yeast extract, has a curative effect in certain cases of tropical macrocytic anemia. This may be due to the presence of a product which is developed as a result of the autolysis and the breaking down of protein. Ungley and James<sup>6</sup> reported that 10 of 18 patients with Addisonian pernicious anemia showed some hematologic response when yeast or wheat germ was administered by mouth. They concluded that "causes other than deficient secretion of the intrinsic factor have contributed to the development of the syndrome." They listed the following possible causes: an inadequate ingestion of the extrinsic factor, a destruction of or an inability to absorb the material which results from the reaction between the intrinsic and extrinsic factors and a failure to store the material in the liver or an increased demand for it, as in pregnancy. They concluded that the extrinsic factor is present in wheat germ and in fresh and autolyzed yeast. There is no parallelism between the amount of vitamin B<sub>2</sub> in yeast and its effect on hematopoiesis in pernicious anemia. Diehl and Kuhnau<sup>7</sup> administered a purified vitamin B<sub>2</sub> preparation alone and after incubation with normal gastric juice to patients with pernicious anemia and did not observe a significant hematopoietic effect. Castle<sup>8</sup> recently stated that he is now fully prepared to relinquish the suggestion that vitamin B<sub>2</sub> is the extrinsic factor. Klumpp and Koletsky<sup>9</sup> thoroughly summarized the literature dealing with the relation of gastric secretion to hematopoiesis. Their paper gives a very complete bibliography of the subject.

Isaacs and Goldhamer<sup>10</sup> emphasized that patients with pernicious anemia have a diminished amount of gastric secretion and suggested that this may be of importance from the standpoint of the etiology of the disease. It was found that the average rate of secretion was 20 cc

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5 Wills, L. Nature of the Hematopoietic Factor in Marmite, *Lancet* **1** 1283, 1933

6 Ungley, C. C. and James, G. V. Effect of Yeast and Wheat Embryo in Anemias. Nature of Haematopoietic Factor in Yeast Effective in Pernicious Anemia, *Quart J Med* **3** 523, 1934

7 Diehl, F., and Kuhnau, J. Ist Vitamin B<sub>2</sub> der therapeutisch wirksame aussere Faktor beim Morbus Biermer? *Deutsches Arch f klin Med* **176** 149, 1933

8 Lassen and Lassen,<sup>4</sup> editor's footnote

9 Klumpp, T. G. and Koletsky, S. The Relation of Gastric Secretion to Hematopoiesis, *Ann Int Med* **8** 991, 1935

10 Isaacs, R., and Goldhamer, S. M. Role of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, *Proc Soc Exper Biol & Med* **31** 706, 1934



per hour in a group of patients with pernicious anemia as compared with an average rate of 150 cc per hour for normal persons. In support of this theory they collected 1,500 cc of gastric juice from five patients with pernicious anemia. One hundred and fifty cc of this was incubated with 200 Gm of meat and was administered to a patient with pernicious anemia daily for ten days. There was a rise of the reticulocyte count and an increase in the hemoglobin content and red blood cell count, which indicated that the gastric secretion of patients with pernicious anemia has some antianemic effect provided it is administered in sufficient quantities. In support of this view it has been determined<sup>11</sup> that there is a direct relationship between the rate of gastric secretion and the level of the red blood cell count in patients with pernicious anemia, that is, the greater the rate of gastric secretion, the higher the red blood cell count.

Recently Morris and his associates<sup>12</sup> reported that the injection intramuscularly, of concentrated gastric juice from a normal person produced a reticulocytic response and a remission in patients with pernicious anemia. It was found that the active principle was heat-labile and was dialyzable through a collodion sac and resisted chemical treatment which was known to destroy enzymes. Fouts, Helmer and Zerfas<sup>13</sup> undertook similar studies and found that when fresh gastric juice from a normal subject was concentrated at icebox temperature by ultrafiltration the material had no antianemic effect when injected intramuscularly into patients with pernicious anemia. When this material, however, was diluted with water and was then concentrated again by vacuum distillation at 40 C it was found to be potent. Furthermore, when the inactive fresh juice was stored in the icebox for two months and was then concentrated by ultrafiltration it had an active antianemic effect. It is thought that gastric juice becomes potent only after some chemical reaction occurs, and the rate at which this proceeds is directly proportional to the temperature of its environment. It has been concluded by some<sup>13</sup> that both the intrinsic and the extrinsic factors are present in normal gastric juice, which reacts to form the substance which is effective in pernicious anemia. Meulengracht<sup>14</sup> undertook to

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11 Goldhamer, S. M. Relationship Between the Gastric Juice Volume and Erythropoiesis in Patients with Untreated Pernicious Anemia, *Proc Soc Exper Biol & Med* **32** 476, 1934.

12 Morris, R. S., Schiff, L., Foulger, J. H., Rich, M. L., and Sherman, J. E. The Treatment of Pernicious Anemia. Effect of a Single Injection of Concentrated Gastric Juice (Addison), *J A M A* **100** 171 (Jan 21) 1933.

13 Fouts, P. J., Helmer, O. M., and Zerfas, L. G. The Formation of a Hematopoietic Substance in Concentrated Human Gastric Juice, *Am J M Sc* **187** 36, 1934.

14 Meulengracht, E. The Presence of the Anti-Anemic Factor in Preparations of Dried Stomach Substance from the Cardia, Fundus and Pylorus Respectively, *Acta med Scandinav* **82** 352, 1934.

determine whether the potent antianemic substance of hog stomach is present in the fundic, pyloric or cardiac region of the stomach. These three areas were carefully separated in fresh hog stomach, prepared in dried, defatted and pulverized form and administered to patients with pernicious anemia. Material obtained from the fundus was inactive. Meulengracht concluded, therefore, that the active principle is not secreted by the surface epithelial cells, the parietal cells or the chief cells. The material made from the pylorus exhibited a striking activity, and it was suggested that the pyloric glands actually secrete the specific substance. The results obtained from the preparation derived from the cardia were inconclusive. It was suggested that pernicious anemia is due to atrophy and inactivity of the pyloric and possibly of the cardiac gland cells. In studying 151 patients with pernicious anemia at necropsy Brown<sup>15</sup> found gross lesions involving the gastro-intestinal tract in 82. In 41 of the 42 instances in which the gastric tissue was examined microscopically there was chronic gastritis with or without a loss of glandular epithelium. In 37 there was a disappearance of acidophilic cells to which is ascribed the associated achylia gastrica.

A number of investigators<sup>16</sup> have made observations which indicate that the liver is an important organ for the storage of the antianemic factor in human beings. It was shown that the liver of patients with pernicious anemia who were adequately treated contained the antianemic principle and that it was absent from the liver of those who were inadequately treated. The importance of the liver as a storage depot is emphasized by the recent work of Goodman, Geiger and Claiborn,<sup>17</sup> who concluded that after total removal of the stomach in the pig there is a progressive loss of antianemic potency of the liver which becomes apparent as early as the third month. They cited their work as confirming that of Bence<sup>18</sup>.

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15 Brown, Madelaine, R. The Pathology of the Gastro-Intestinal Tract in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord. A Study of One Hundred and Fifty-One Autopsies, *New England J Med* **210** 473, 1934.

16 Richter, O., Ivy, A. C., and Kim, M. S. Action of Human "Pernicious Anemia Liver Extract," *Proc Soc Exper Biol & Med* **29** 1093, 1932. Wilkinson, J. F., and Klein, L. The Hemopoietic Activity of Normal and Abnormal Human Liver with Special Reference to Pernicious Anemia, *Quart J Med* **3** 341, 1934. Goldhamer, S. M., Isaacs, R., and Sturgis, C. C. The Role of the Liver in Hematopoiesis, *Am J M Sc* **188** 193, 1934.

17 Goodman, L., Geiger, A. J., and Claiborn, L. N. Anti-Anemic Potency of Liver After Gastrectomy in Swine, *Proc Soc Exper Biol & Med* **32** 810, 1935.

18 Bence, J. Die Rolle des Magens und der Leber in der Pathologie der perniziösen Anämie, *Ztschr f klin Med* **126** 127, 1933.

## ACHYLIA GASTRICA

The acidity of normal gastric juice was demonstrated in 1780, and the absence of free hydrochloric acid in the gastric juice of patients with pernicious anemia was noted in 1886. The latter observation has been verified by innumerable investigators. With the advent of the fractional method of gastric analysis in 1914 and the demonstration of the value of injections of histamine it was possible to evaluate more accurately the achlorhydric condition and to emphasize further the profound secretory dysfunction in pernicious anemia.

Apparently there are two schools of thought regarding achlorhydria in pernicious anemia. While many writers have stressed the point that the presence of free hydrochloric acid is not compatible with the diagnosis of true pernicious anemia,<sup>19</sup> others have reported exceptional cases of pernicious anemia in which free acid was present in the gastric juice.<sup>20</sup> In the light of the recent developments of the pathologic physiology of macrocytic anemia and the newer methods of gastric analysis the diagnosis in many of these cases may be questioned. Likewise, the reports of the return of free hydrochloric acid in cases of pernicious anemia in induced remission should be more closely investigated, as the general consensus is that there is no return of this function,<sup>21</sup> although there is an increase in the volume of gastric juice and a suggested increase in the amount of intrinsic factor.<sup>22</sup>

Fractional gastric analyses with injections of histamine have revealed several interesting findings. Apparently there is no demonstrable deficiency in salivary amylase in patients with pernicious anemia.<sup>23</sup>

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19 (a) Haden, Russell L. Macrocytosis of the Erythrocytes and Achlorhydria in Pernicious Anemia, *J A M A* **98** 202 (Jan 16) 1932 (b) Bockus, H L, Bank, J, and Willard, J H. Achlorhydria with Review of Two Hundred and Ten Cases in Patients with Gastro-Intestinal Complaints, *Am J M Sc* **184** 185, 1932 (c) Hartfall, Stanley, J. The Secretion of Gastric Juice in Response to Histamine in Addisonian Anaemia, *Guy's Hosp Rep* **83** 37, 1933 (d) Simpson Memorial Institute. Unpublished data (e) Wilkinson, John F. The Gastric Secretion in Pernicious Anemia, *Quart J Med* **1** 361, 1932

20 Barnett, C W. The Significance of the Gastric Secretions in Pernicious Anemia, *Am J M Sc* **182** 170, 1931. Levin, A L. The Occurrence of a Pernicious Anemia Syndrome in the Presence of Normal Gastric Acidity, *Am J Digest Dis & Nutrition* **1** 240, 1934. Castle, Heath and Strauss.<sup>1d</sup> Wilkinson.<sup>19e</sup>

21 Davidson, L S P. Pernicious Anaemia with Return of Hydrochloric Acid and Ferments After Treatment, *Brit M J* **1** 182, 1933. Wilkinson.<sup>19e</sup>

22 Goldhamer, S M, Isaacs, R, and Sturgis, C C. The Quantitative Relationship Between the Amount of the "Intrinsic Factor of Castle" and the Maturation of Red Blood Cells in Patients with Pernicious Anemia, *J Clin Investigation*, to be published.

23 Emerson, C P and Helmer, O M. A Study of the Salivary Amylase in Patients with Pernicious Anemia, *J Lab & Clin Med* **19** 504, 1934.

Both the gastric juice after fasting and the specimens obtained following stimulation with histamine are markedly decreased in volume, and the mucus may be increased, normal or diminished,<sup>24</sup> there is no free hydrochloric acid present, the total acid is decreased<sup>25</sup> and pepsin and rennin are absent or present in negligible amounts,<sup>26</sup> the total chloride content is reduced,<sup>26a</sup> the value for protein nitrogen is increased, and that for nonprotein nitrogen is within normal limits<sup>27</sup> Injections of histamine, acetylcholine and physostigmine have practically no effect on altering the gastric secretion in patients with pernicious anemia<sup>28</sup> The duodenal contents reveal the presence of pancreatic enzymes, although the amount may be reduced<sup>26a</sup> The latter observation has been questioned<sup>29</sup>

The truth of the preceding findings has been substantiated by an analysis of the tissue obtained from patients with pernicious anemia<sup>30</sup> An analysis of the gastric mucosa revealed the absence of proteolytic enzymes The pancreatic specimens contained a normal amount of tryptic, amolytic and proteolytic enzymes The duodenal tissue contained a sufficient amount of enterokinase In weighing all the evidence submitted it appears that pernicious anemia is associated with true achylia gastrica

#### MANIFESTATIONS DUE TO LESIONS IN THE SPINAL CORD AND BRAIN

It is the universal opinion that degeneration of the spinal cord and the brain in cases of pernicious anemia is a part of the disease process Some authors have reported the occurrence of involvement of the spinal

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24 (a) Helmer, O M , Fouts, P J , and Zerfas, L G Gastro-Intestinal Studies, Gastric Juice in Pernicious Anemia, *J Clin Investigation* **11** 1129, 1932 (b) Hartfall<sup>19c</sup> (c) Wilkinson<sup>19e</sup>

25 Helmer, Fouts and Zerfas<sup>24</sup> Footnote 19

26 Helmer, O M , Fouts, P J , and Zerfas, L G (a) Gastro-Intestinal Studies Pancreatic Enzymes in Pernicious Anemia, *J Clin Investigation* **12** 519, 1933, (b) Gastro-Intestinal Studies The Relation of  $p_H$  to the Pepsin and Rennin Content of the Gastric Juice, *Am J Digest Dis & Nutrition* **1** 120, 1934 (c) Wilkinson<sup>19e</sup>

27 Burger, G N , Hartfall, S J , and Witts, L J The Secretion of Mucus by the Stomach with Special Reference to Achlorhydric Anaemias, *Guy's Hosp Rep* **83** 497, 1933

28 Wilkinson, John F The Action of Acetylcholine on the Gastric Secretion in Man, *Brit J Exper Path* **13** 141, 1932 Burger, Hartfall and Witts<sup>27</sup> Hartfall<sup>19c</sup>

29 Cheney, G , and Niemand, F A Possible Relationship of Pancreatic Insufficiency to Addison-Biermer (Pernicious) Anemia, *Arch Int Med* **49** 925 (June) 1932

30 Helmer, O M , Fouts, P J , and Zerfas, L G Gastro-Intestinal Studies Determination of Enzymes on Autopsy Specimens from Cases of Pernicious Anemia and Pellagra, *Arch Int Med* **53** 675 (May) 1934

cord in 90 per cent or more of their cases,<sup>31</sup> while others have noted it in less than 25 per cent.<sup>32</sup> The majority of investigators, however, are of the opinion that more than 70 per cent of the patients exhibit neurologic manifestations.<sup>33</sup> These figures have been supported by autopsy findings.<sup>34</sup> With the advent of antianemia therapy the incidence of involvement of the central nervous system is increasing.<sup>35</sup>

Although cerebral changes were noted first by Addison in his classic description, their importance has received too little attention. Recently several authors have stressed the frequent occurrence of cerebral changes, noting their presence in over 60 per cent of the patients with pernicious anemia.<sup>36</sup>

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31 (a) Ahrens, R. S. Neurologic Aspects of Primary Anemia, *Arch Neurol & Psychiat* **28** 92 (July) 1932. (b) Smithburn, R. C., and Zervas, L. G. The Neural Symptoms and Signs in Pernicious Anemia. Effects of Liver Extract, *ibid* **25** 1100 (May) 1931. (c) Goldhamer, S. M., Bethell, F. H., Isaacs, R., and Sturgis, C. C. The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, *J. A. M. A.* **103** 1663 (Dec 1) 1934.

32 Young, Richard H. Neurologic Features of Pernicious Anemia, *J. A. M. A.* **99** 612 (Aug 30) 1932.

33 Baker, B. M., Jr., Bordley, J., III, and Longcope, W. T. (a) The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, *Am J M Sc* **184** 1, 1932. (b) The Effect of Liver and Liver Extract upon the Symptoms and Signs Referable to the Nervous System in Pernicious Anemia, *Minnesota Med* **13** 815, 1930. (c) Grinker, R. R. Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, *Arch Int Med* **38** 292 (Sept) 1926. (d) Reese, Hans H., and Beigler, S. K. Subacute Combined Degeneration of the Spinal Cord and Pernicious Anemia, *Am J M Sc* **171** 194, 1926. (e) Riley, W. H. A Clinical Study of Two Hundred and Sixty-Four Cases of Pernicious Anemia with Special Reference to the Involvement of the Central Nervous System, *Bull Battle Creek San & Hosp Clin* **18** 195, 1923. (f) Ungley, C. C., and Suzman, M. M. Subacute Combined Degeneration of the Cord, Symptomatology and Effects of Liver Therapy, *Brain* **52** 271, 1929.

34 Hadfield, G. The Central Nervous System in Addisonian Anemia, *Bristol Med-Chir J* **44** 21, 1927.

35 Kiely, Charles. Neurologic and Psychopathic Manifestations of Pernicious Anemia, *J. Michigan M Soc* **31** 272, 1932. Young<sup>32</sup>

36 (a) Lurie, Louis A. Pernicious Anemia with Mental Symptoms. Observations on Varying Extent and Probable Duration of Central Nervous System Lesions in Four Necropsied Cases, *Arch Neurol & Psychiat* **2** 67 (July) 1919. (b) McAlpine, Douglas. A Review of the Nervous and Mental Aspects of Pernicious Anemia, *Lancet* **2** 643, 1929. (c) Piney, A. Mental Changes Associated with Pernicious Anaemia, *J. Neurol & Psychopath* **13** 127, 1932. (d) Skoog, A. L. Neurologic Manifestations in Pernicious Anemia, *J. A. M. A.* **87** 1957 (Dec 11) 1926. (e) Smith, Lauren H. Mental and Neurologic Changes in Pernicious Anemia. Report of Case with Treatment by Minot-Murphy Diet, *Arch Neurol & Psychiat* **22** 551 (Sept) 1929. (f) Warburg, E. J., and Jorgensen, S. Psychoses and Neurastheniae Associated with Achylia Gastrica and Megalocytosis and Relation Between This Syndrome and Pernicious Anemia. One Psychosis, *Acta med Scandinav* **69** 537, 1928, *Hospitaltid* **71** 974, 1928. (g) Footnotes 31, 32 and 33a, b, c, d.

The etiology of the changes in the nervous system remains obscure. The old theory of a neurotoxin as the causal factor is supported by many.<sup>37</sup> More recently, as a result of experimental evidence, it is believed that the manifestations in the cord may result from a vitamin deficiency,<sup>38</sup> others maintain that there is a disturbance in lipid metabolism, and still others support the view that the changes are related to the anemia.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, ataxia, loss of finer coordination of the fingers and disturbances of the bladder.<sup>31c</sup> The character of the signs depends on whether the changes in the posterior or in the lateral columns of the cord predominate. The reflexes may be increased, decreased or lost. The outstanding sign is a disturbance in the vibratory sensation. Any of the cranial nerves may be involved, but this is relatively rare.<sup>31a</sup> Manifestations of cerebral involvement vary from mild irritability to severe mania, they may be present alone or in association with disturbances of the cord, with or without evidence of anemia, and they may present themselves as the earliest and only manifestation of pernicious anemia.

Conclusions drawn from the benefits of therapy must be guarded, as it is known that there may be spontaneous variations in the intensity of the neurologic manifestations without treatment. Many authors have reported distinct improvement with large doses of liver,<sup>39</sup> others have recommended the administration of desiccated stomach, liver extract

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37 Camac, C N B, and Milne, L S. The Spinal Cord Lesions in Two Cases of Pernicious Anemia, *Am J M Sc* **140** 563 (Oct) 1910.

38 Gilda, E F, Kattwinkel, E E, and Castle, W B. Experimental Combined System Disease, *New England J Med* **202** 523, 1930. Suzman, M M, Muller, G L, and Ungley, C C. An Attempt to Produce Spinal Cord Degeneration in Dogs Fed a High Cereal Diet Deficient in Vitamin A. The Incidental Development of a Syndrome of Anemia, Skin Lesions, Anorexia, and Changes in the Concentration of Blood Lipoids, *Am J Physiol* **101** 529, 1932.

39 (a) Davison, Charles. Spinal Cord Changes in Subacute Combined Degeneration Following Liver Therapy. Histopathologic Study, *Proc Soc Exper Biol & Med* **28** 639, 1931. (b) Farquharson, Ray F, and Graham, Duncan. Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, *Canad M A J* **23** 237, 1930. (c) Fried, B M. Subacute Combined Degeneration of Spinal Cord in Pernicious Anemia. Treatment with Liver Diet, *J A M A* **92** 1260 (April 13) 1929. (d) Garvey, P H, Levin, P M, and Guller, E I. Effect of Liver Therapy on the Neurologic Aspects of Pernicious Anemia, *Ann Int Med* **6** 1441, 1933. (e) Minot, George R. The Treatment of Anemia, with Comments on Food Deficiency and Its Relation to the Nervous System, *Tr Am Neurol A* **57** 329, 1931. (f) Starr, Paul. The Prevention of Spinal Cord Degeneration in Pernicious Anemia (Cases with Progression of Cord Symptoms), *J A M A* **96** 1219 (April 11) 1931. (g) Suzman, M M. Effects of Liver Therapy in One Hundred Cases of Subacute Combined Degeneration of the Cord, *Tr Am Neurol A* **57** 339, 1931. (h) Footnotes 31a, 33f and 36c.

(orally and parenterally),<sup>40</sup> preparations of iron,<sup>41</sup> vitamins,<sup>42</sup> solution of potassium arsenite and brain substance<sup>43</sup>

Antianemia therapy, when given in a sufficient amount, does not have a specific curative effect on degeneration of the spinal cord but contributes indirectly to the improvement of the neurologic manifestations. The primary effect is an improvement in the general feeling of well-being of the patient.

In analyzing the results of the various investigators it is apparent that symptomatic improvement occurs in about 50 per cent of the patients, but rarely, if ever, is there any improvement in the signs. Manifestations referable to the posterior columns respond more readily than do those due to lesions of the lateral columns.<sup>44</sup> If the cerebral changes are a result of the disease process, improvement may be anticipated,<sup>45</sup> however, if a psychosis exists independent of pernicious anemia, no improvement can be expected.

#### TREATMENT

Experience of many workers during the past eight years has confirmed the hematopoietic activity of the following agents in the treatment of pernicious anemia: liver, liver extracts administered by mouth and intramuscularly<sup>46</sup> and intravenously,<sup>47</sup> desiccated, defatted

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40 Footnotes 31b and 33a

41 Sargant, Will. Treatment of Subacute Combined Degeneration of Cord by Massive Iron Dosage, *Lancet* **1** 230, 1932. Snowman, L. V. A Case of Combined Degeneration of the Cord Treated with Massive Dosage of Iron, *ibid* **1** 613, 1932.

42 Fouts, P. J., Kempf, G. F., Greene, J. A., and Zervas, L. G. Vitamin B Intravenously for Treatment of Neurological Changes in Pernicious Anemia, *J. Indiana M. A.* **25** 448, 1932. Footnote 39a.

43 Ungley, Charles C. Effect of Brain Diet in Pernicious Anemia, *Lancet* **2** 63, 1931. Effect of Brain Diet in Subacute Combined Degeneration of Cord, *ibid* **1** 227, 1932.

44 Footnotes 31a, 34 and 39b.

45 Tenney, C. F., and Goldstein, Eli. Mental Symptoms of Pernicious Anemia and Their Response to Liver Therapy, *M. Clin. North America* **17** 185, 1933. Footnotes 31c and 36c and c.

46 Strauss, M. B., and Castle, W. B. Parenteral Liver Therapy in the Treatment of Pernicious Anemia, *J. A. M. A.* **98** 1620 (May 7) 1932. Conner, H. M. Injection of Liver Extract in Treatment of Pernicious Anemia, *ibid* **99** 614 (Aug. 20) 1932. McHenry, E. W., Mills, E. S., and Farquharson, R. F. Treatment of Pernicious Anemia by the Intramuscular Administration of Liver Extract, *Canad. M. A. J.* **28** 123, 1933. Murphy, W. P. The Parenteral Use of Liver Extract in Pernicious Anemia, *J. A. M. A.* **98** 1051 (March 26) 1932.

47 Isaacs, R., Sturgis, C. C., Goldhamer, S. M., and Bethell, F. H. The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, *J. A. M. A.* **100** 629 (March 4) 1933. Fouts, Paul J., and Zervas, L. G. Use of Liver Extract Intravenously. Report of Ten Cases, *Arch. Int. Med.* **50** 27, 1932. Freeman, E. T. Intravenous Liver Therapy in Pernicious Anemia, *Irish J. M. Sc.*, April 1932, p. 182.

stomach,<sup>48</sup> and concentrated gastric juice administered intramuscularly<sup>49</sup> The cases of patients who received liver therapy for nine and one-half, eight and seven years, respectively, have been described<sup>50</sup> The potency of liver extract may be increased by incubation with gastric tissue<sup>51</sup> or gastric juice<sup>52</sup> Some of the components of the vitamin B complex may play a part in the gastric formation of hematopoietically active substances<sup>53</sup> Gastric juice from the fourth stomach of adult cattle is a source of the extrinsic factor<sup>54</sup>

It has been suggested that intensive iron therapy in conjunction with the administration of liver substances may be of value in reducing the neurologic symptoms<sup>55</sup>

Massive doses of liver extract may hasten the onset of the reticulo-cyte response within certain physiologic limits<sup>56</sup> Among the types of

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48 Wilkinson, J F Antianaemic Principle in Stomach Tissue, *Proc Roy Soc Med* **26** 1341, 1933 Sturgis, C C, and Isaacs, R Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract, *Ann Int Med* **5** 131, 1931

49 Morris, R S, Schiff, Leon, Burger, G, and Sherman, J E A Specific Hematopoietic Hormone in Normal Gastric Juice, Preliminary Report, *J A M A* **98** 1080 (March 26) 1932

50 Gibson, R B, and Fowler, W M Effects of Prolonged Liver Dietary in Pernicious Anemia Case Reports of Three Patients Receiving Liver Therapy for Nine and a Half, Eight, and Seven Years, Respectively, *Arch Int Med* **50**. 124, (July) 1932

51 Walden, G B, and Clowes, G H A Pernicious Anemia Method Whereby Therapeutic Efficiency of Liver and Liver Fractions May Be Substantially Increased, *Proc Soc Exper Biol & Med* **29** 873, 1932 Barnett, C W, and Thebaut, W M, Jr Treatment of Pernicious Anemia with Digested Liver, *J A M A* **99** 556 (Aug 13) 1932 Conner, H M Preparation of Liver and Stomach (Extralim) in the Treatment of Pernicious Anemia, *M Clin North America* **18** 385, 1934

52 Helmer, O M, Fouts, P J, and Zerfas, L G Increased Potency of Liver Extract by Incubation with Human Gastric Juice, *Proc Soc Exper Biol & Med* **30** 775, 1933

53 (a) Conner, H M Extract of Fish Liver in Treatment of Pernicious Anemia Treatment of Pernicious Anemia with Diet Rich in Vitamines, *M Clin North America* **15** 463, 1932 (b) Strauss, M B, and Castle, W B The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, Activation of Yeast Derivatives with Normal Human Gastric Juice, *New England J Med* **207** 55, 1932 (c) Goodall, A Treatment of Pernicious Anaemia by Marmite, *Lancet* **2** 781, 1932

54 Williams, H A, and Vander Veer, J B Demonstration of Anti-Anemic Factor in Bovine Gastric Juice, *Proc Soc Exper Biol & Med* **29** 858, 1932

55 Sargent, W Treatment of Subacute Combined Degeneration of Cord by Massive Iron Dosage, *Lancet* **1** 230, 1932

56 Connery, J E, and Goldwater, L J Studies on Patients with Pernicious Anemia Treated with Massive Doses of Liver Extract Effect on Reticulocytes, Red Cells, Hemoglobin and White Cells, *J Lab & Clin Med* **17** 1016, 1932



liver found to be effective are preparations from cattle, horse,<sup>57</sup> fish<sup>58</sup> pig and dog<sup>59</sup>

Nuclear extractives from the red blood cells of fowl are active in inducing a remission when taken by mouth<sup>60</sup> Autolyzed liver has been reported as being more active than fresh liver,<sup>61</sup> but recent work has not confirmed this<sup>62</sup>

The intramuscular method of administration is preferred for those patients who are unable to retain food or who do not absorb material from the gastro-intestinal tract properly<sup>63</sup>

Intra-ossal injection of liver has been suggested<sup>64</sup>

Minot<sup>65</sup> emphasized the importance of giving medication on a quantitative basis, judging the requirements of each patient separately Some patients require from two to three times the dosage of others<sup>66</sup> Transfusion of blood is suggested when the blood count is very low and infection or other complication is present<sup>67</sup> Dilute hydrochloric acid with meals is advocated only for those patients who have gastric distress after meals<sup>68</sup> As a check for the efficiency of treatment of the

57 Meyer, A E , Richter, O , and Ivy, A C Pernicious Anemia Treatment with Equine Liver Extract Injectable Either Subcutaneously or Intravenously, *Arch Int Med* **50** 538 (Oct) 1932

58 Davidson, L S P Treatment of Pernicious Anaemia with Fish-Liver Extract, *Brit M J* **2** 347, 1932 Footnote 53a

59 Strauss, M B , and Castle, W B Amount of Material Effective in Pernicious Anemia Present in Dog Liver, *Proc Soc Exper Biol & Med* **31** 360, 1933

60 Jones, N W , Phillips, B I , and Larsell, O Hemopoietic Effect of Nuclear Extractives from Red Blood Cells of Fowl in Pernicious Anemia, *North-west Med* **31** 380, 1932

61 Herron, W F , and McElroy, W S The Use of Autolyzed Liver in the Treatment of Pernicious Anemia A Preliminary Clinical Report, *J A M A* **100** 1084 (April 8) 1933

62 Castle, W B , and Strauss, M B Effect of Autolysis on Potency of Liver in Treatment of Pernicious Anemia, *J A M A* **104** 798 (March 9) 1935

63 Connery, J E , and Goldwater, L J Parenteral Use of Liver Extract in Treatment of Pernicious Anemia, *J A M A* **98** 1060 (March 26) 1932 Owen, A , and Anderson, D Pernicious Anemia Treated with Liver Extract Given Intramuscularly, *M J Australia* **2** 572 1932 Alt, H L Maintenance Dose of Parenteral Liver Extract in Treatment of Pernicious Anemia, *Proc Soc Exper Biol & Med* **30** 565, 1933

64 Josefson, Arnold A New Method of Treatment—Intraossal Injections, *Acta med Scandinav* **81** 550, 1934

65 Minot, G R The Importance of the Treatment of Pernicious Anemia on a Quantitative Basis, *J A M A* **99** 1906 (Dec 3) 1932

66 Kloster, J Einige Erfahrungen uber die Dosierung des Campolons bei der Biermerschen Anemie, *Acta med Scandinav* **79** 475, 1933

67 Sturgis, C C , and Isaacs, R Pernicious Anemia Its Nature and a Consideration of Recent Advances in the Treatment of the Disease, *California & West Med* **39** 73, 1933

68 Sturgis, C C , and Isaacs, R Treatment of Pernicious Anemia, *North-west Med* **31** 1, 1932

blood, Haden<sup>69</sup> recommended the determination of the size of the red blood cells. Treatment is inadequate as long as there is macrocytosis.

#### MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

There appear to be five factors which may produce a macrocytic anemia. It is generally accepted that the substance necessary for the maturation of red blood cells is formed from the interaction of (1) an extrinsic factor (food) and (2) an intrinsic factor present in the stomach. The resulting product is (3) absorbed from the intestine, (4) stored in the liver and (5) released to the body tissues for utilization when needed. Any disturbance of this mechanism at the point indicated by the numbers will produce a macrocytic anemia.

Although vitamin B<sub>12</sub> has been proved not to be the extrinsic factor in pernicious anemia, a commercially prepared autolyzed yeast extract has been of value for treatment of macrocytic anemia of pregnancy, tropical anemia and experimental macrocytic anemia resulting from a deficient diet in vitamin B<sub>12</sub>.<sup>70</sup> If for any reason, known or unknown, the intrinsic factor present in the stomach is diminished<sup>71</sup> or destroyed, a macrocytic anemia simulating pernicious anemia may develop. Cases of pernicious-like anemia have been reported following chronic alcoholism,<sup>72</sup> syphilis and cancer of the stomach,<sup>73</sup> gastrectomy<sup>74</sup> and

69 Haden, R. L. Complete Treatment of Pernicious Anemia, *Am J Digest Dis & Nutrition* **1** 628, 1934.

70 Wills, L. Note on Use of Marmite (Yeast Extract) in Tropical Macrocytic Anemias, Including Pernicious Anemia of Pregnancy, *Indian M Gaz* **68** 133, 1933, Treatment of Pernicious Anaemia of Pregnancy and "Tropical Anemia" with Special Reference to Yeast Extract (Marmite) as Curative Agent, *Brit M J* **1** 1059, 1931. Witts, L. J., Fairley, N. H., and Goodhar, G. Discussion on Megalocytic Anemias of Tropical and Non-Tropical Countries, *Proc Roy Soc Med* **25** 1703, 1932. Wills, L., and Bilimoria, H. S. Pernicious Anemia of Pregnancy. Production of Macrocytic Anemia in Monkeys by Deficient Feeding (Curative Effect of Marmite), *Indian J M Research* **20** 391, 1932. Rhoads, C. P., and Miller, D. K. Production in Dogs of Chronic Black Tongue with Anemia, *J Exper Med* **58** 585, 1933.

71 (a) Goldhamer, S. M., and Isaacs, R. Role of Decreased Amount of Gastric Secretion in Production of Pernicious Anemia, *Proc Soc Exper Biol & Med* **31** 706, 1934. (b) Goldhamer, S. M. Relationship Between Gastric Juice Volume and Erythropoiesis in Patients with Untreated Pernicious Anemia, *ibid* **32** 376, 1934. (c) Strauss, M. B., and Castle, W. B. Studies of Anemia in Pregnancy. Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and Treatment of These Conditions, *Am J M Sc* **185** 539, 1933.

72 Torrey, R. G. Anemia Due to Gastritis Occasioned by Alcoholism, Consideration of Cases of Purpura, Including Example of Purpura Apparently Secondary to Pernicious Anemia, *M Clin North America* **17** 603, 1933.

73 Conner, H. M., and Birkeland, I. W. Coexistence of Pernicious Anemia and Lesions of Gastro-Intestinal Tract. Carcinoma of Stomach, Consideration of Twenty Cases. Eleven Reported, *Ann Int Med* **7** 89, 1933.

pregnancy<sup>71c</sup> The occurrence of macrocytic anemia has also been reported in many instances in which there was a dysfunction of absorption from the intestinal tract Obstruction of the small intestine, tapeworm, celiac disease, gastrocolic fistula and sprue have all been observed in association with macrocytic anemia<sup>75</sup> Study of the bone marrow in some cases of sprue, during relapse and remission, revealed a striking similarity to the pathologic changes associated with pernicious anemia<sup>76</sup>

Following the experimental work<sup>77</sup> which proved the liver to be the storehouse of the material necessary for the maturation of red blood cells there were several references to an anemia with a high color index occurring in association with disease of the liver<sup>78</sup> There appears to

74 Goldhamer, S M The Pernicious Anaemia Syndrome in Gastrectomized Patients, *Surg, Gynec & Obst* **57** 257, 1933 Rowlands, R A, and Simpson, S Levy Addisonian Anemia Following Gastrectomy and Gastro-Jejunostomy, *Lancet* **2** 1202, 1932 Ungley, C C A Case of Complete Gastrectomy Followed by Pernicious Anaemia, *Newcastle M J* **12** 192 (Oct) 1932

75 Hurst, A F Case of Addison's Anemia with Subacute Combined Degeneration of Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of Ileum, *Guy's Hosp Rep* **83** 47, 1933 Birkeland, I W "Bothriocephalus Anemia", *Diphyllobothrium Latum* and Pernicious Anemia, *Medicine* **11** 1, 1932 Mills, E S Anaemia from *Diphyllobothrium Latum*, *Canad M A J* **25** 75, 1931 Magath, T B Bothriocephalus Anemia (Anemia Caused by *Diphyllobothrium Latum*), *Proc Staff Meet, Mayo Clin* **5** 124, 1930 Vaughan, J M, and Hunter, D Treatment by Marmite (Yeast Extract) of Megalocyte Hyperchromic Anemia Occurring in Idiopathic Steatorrhea (Celiac Disease), *Lancet* **1** 829, 1932 Fairley, N H, and Kilner, T P Gastro-Jejuno-Colic Fistula, with Megalocytic Anemia Simulating Sprue, *ibid* **2** 1335, 1931 Barker, L F A Few of the Cases Selected for Study on Ward Rounds Illustrating Method of Procedure, *Internat Clin* **3** 26, 1931 Rogers, L, and Cooke, W E Resistant Sprue Anemia Yielding to Intravenous Liver Therapy, *Brit M J* **1** 272, 1932 Vaidya, S K Observations on Pernicious-Type Anemias in Tropics, and Disease Called Sprue, *J Trop Med* **33** 265, 1930

76 Rhoads, C P, and Castle, W B Pathology of Bone Marrow in Sprue Anemia, *Am J Path (supp)* **9** 813, 1933

77 (a) Richter, O, Ivy, A C, and Kim, M S Action of Human "Pernicious Anemia Liver Extract," *Proc Soc Exper Biol & Med* **29** 1093, 1932 (b) Goldhamer, S M, Isaacs, R, and Sturgis, C C The Role of Liver in Hematopoiesis, *Am J M Sc* **188** 193, 1934

78 Wintrobe, M M, and Shumacher, H S, Jr Occurrence of Macrocytic Anemia in Association with Disorder of Liver, Together with Consideration of Relation of This Anemia to Pernicious Anemia, *Bull Johns Hopkins Hosp* **52** 387, 1933 Goldhamer, S M Liver Extract Therapy in Cirrhosis of the Liver, Relation of Liver Dysfunction to Nonstorage of "Anti-Anemic" Substance in Producing a Blood Picture Resembling Pernicious Anemia in a Patient Secreting Free Hydrochloric Acid, *Arch Int Med* **53** 54 (Jan) 1934 Van Duyn, J Macrocytic Anemia in Disease of Liver, *ibid* **52** 839 (Dec) 1933 Wright, D O Macrocytic Anemia and Hepatic Cirrhosis, *Am J M Sc* **189** 115, 1935 Wright, D O Macrocytic Anemia in Banti's Disease, *Ann Int Med* **8** 814, 1935 Foot-note 77b

be sufficient evidence that the intrinsic factor may be present in the stomach, but because of damage to the liver the hematopoietic substance cannot be stored and released to the body for utilization, and as a result macrocytic anemia develops

The treatment of anemia associated with these various conditions depends on which factor or factors are contributing to the cause in each given instance. If the intrinsic or extrinsic factor is absent, liver administered orally may be appropriate, however, if there is a disturbance of absorption or storage, parenteral therapy should be instituted.

#### ANEMIA OF PREGNANCY

Strauss<sup>79</sup> emphasized that the physiologic anemia of normal pregnant women consists of a steady decline in the red blood cell count and hemoglobin content from early in pregnancy until the end of the second trimester, after which no further change or a slight rise occurs. About ten days after parturition the blood returns to the level prior to pregnancy provided there is no defect in diet or gastric secretion. A study of the volume of the blood during pregnancy indicated that this condition is not anemia in the strict sense but merely hydremia.

Strauss stated further that a woman with one of any number of diseases which may cause anemia may become pregnant and the anemia associated with the pregnancy may be nothing more than a coincidence. This is true in cases of infection, leukemia and cancer. Moreover, pregnancy may be associated with toxemia, hemorrhage, nephritis and puerperal sepsis, any one of which may produce anemia.

When these known causes of anemia are disregarded, however, there still remain two types of anemia of pregnancy of unknown etiology. One is hypochromic (chlorotic or simple secondary anemia, idiopathic hypochromic anemia) and the other, macrocytic (pernicious).

Thirty patients with idiopathic hypochromic anemia of pregnancy, all of whom had a hemoglobin content of less than 45 per cent (Sahli), were studied from the standpoint of gastric secretory defects and the character of the diets of which they had partaken. It was found that all of these patients had anacidity or hypo-acidity or had been eating a diet which was inadequate in iron-containing foods. In some instances both the diet was poor and there was a deficiency of gastric acidity. Another factor in the production of anemia is the loss of hemoglobin-building material from the mother which must be used for synthesis of the fetal hemoglobin. When the patients were given 6 Gm of iron and ammonium citrate daily there was a prompt return of the hemoglobin content and red blood cell count to normal.

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<sup>79</sup> Strauss, M. B. Etiology and Treatment of Anemia in Pregnancy, *J. A. M. A.* **102** 281 (Jan 27) 1934.

Ten patients with macrocytic anemia were studied by Strauss. These patients all had a red blood cell count under 2,500,000 per cubic millimeter, and, in addition to the usual symptoms of anemia, gastrointestinal complaints and fever were observed in a majority of them. Glossitis was present in 4 patients and splenomegaly in 2. One patient had mild combined degeneration of the spinal cord. The blood picture closely simulated that of true addisonian pernicious anemia. In 5 patients there was achlorhydria, in 4, hypochlorhydria, and in 1, normal acidity of the gastric juice, following the injection of histamine. All but 1 of these patients gave a history of a limited intake of food containing animal protein. The administration of 200 Gm of beefsteak daily resulted in some improvement, but a greater effect was produced by giving 150 cc of normal gastric juice incubated with the beefsteak. It was concluded that patients with this type of anemia have both defects in gastric secretion and diets which have a deficiency chiefly in animal protein. The former is an etiologic factor similar to that associated with true addisonian pernicious anemia. This type of anemia is relieved by the administration of liver extract, either orally or parenterally.

It has been determined<sup>80</sup> that pregnant women who have hypochromic anemia bear infants with a normal blood picture at birth. In the latter, however, there develops anemia of varying severity during the first year of life. The anemia of the mother may be corrected by iron therapy during pregnancy, in which case the infant will not have anemia after birth. It is believed that this form of anemia in the infant is due to the inability of the fetus to accumulate sufficient reserves of iron, owing to a deficiency of this element in the maternal organism.

The volume of the blood and plasma has been systematically studied in a number of women from early pregnancy throughout the puerperium.<sup>81</sup> The plasma volume was determined by means of the vital red technic. It was found that the volume of the blood and that of the plasma increase during the first trimester until by the thirteenth week the gain amounts to 16 and 18 per cent, respectively. There is an average increase of 23 per cent in the blood volume and of 25 per cent in the plasma volume at term. Partly on account of the increase in the blood volume, but especially on account of the tremendous amount of fluid in her tissues, the pregnant woman survives losses of blood which would be fatal to a nonpregnant person. There is a decrease of 16 per cent in both the blood and the plasma volume eight weeks post partum. Dieckmann and Wegner interpreted the increase in the volume of the

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80 Strauss, M. B. Anemia of Infancy from Maternal Iron Deficiency in Pregnancy, *J. Clin. Investigation* **12** 345, 1933.

81 Dieckmann, W. J., and Wegner, Carl R. The Blood in Normal Pregnancy. I. Blood and Plasma Volumes, *Arch. Int. Med.* **53** 71 (Jan.) 1934.

blood and plasma as an attempt of the body to fill the vessels and as "probably a part of the mechanism required to permit proper fetal respiration"

## ANEMIA ASSOCIATED WITH OTHER DISEASE ENTITIES

### HEMOLYTIC JAUNDICE

Clinically, hemolytic jaundice of the congenital type is characterized by anemia, enlargement of the spleen, jaundice, a history of exacerbations and remissions, microcytosis, spherocytosis, increased fragility of the red blood cells and constant reticulocytosis<sup>82</sup> The anemia, jaundice, splenomegaly and increase in the young red blood cells are probably secondary to the increased destruction of blood resulting from the abnormal fragility of the erythrocytes<sup>83</sup> Often, hemolytic icterus is complicated with ulcers, osseous changes and gallstones<sup>84</sup>

The etiology of the disease remains theoretical The change in the size and shape of the red blood cells is thought by some to be a hereditary expression of the disease, others are of the opinion that the alteration in the red blood cells is due to lessened vitality of the cells, still others believe that there is a primary defect in the bone marrow, and, finally, some observers suggest that the small red blood cells and increased fragility are phenomena of regeneration secondary to the increased activity of the bone marrow

Although microcytosis has been recognized in hemolytic jaundice for many years, it is only recently that spherocytosis has been emphasized in this condition, and it can best be shown by the increase in the volume-thickness index<sup>83</sup> Normal erythrocytes, when placed in hypotonic salt solution, become progressively more spherical with practically no alteration in the diameter as the solution is made more hypotonic Just preceding hemolysis the cells assume their most globular form In congenital hemolytic jaundice many of the erythrocytes are already spherical and hence are nearer the point of hemolysis It has been concluded from these experiments that there is a direct relation between the volume-thickness index and the fragility of the red blood cells

Chronic cholecystitis and cholelithiasis have been reported in 68 per cent of the cases of hemolytic jaundice<sup>84b</sup> The differential diagnosis is thus quite confusing Congenital acholuric jaundice must also be

82 Barron, M Differential Diagnosis of Jaundice with Special Reference to Congenital Hemolytic Jaundice, *Minnesota Med* **15** 479, 1932

83 Haden, R L The Mechanism of the Increased Fragility of the Erythrocytes in Congenital Hemolytic Jaundice, *Am J M Sc* **188** 441, 1934

84 (a) Cheney, W F, and Cheney, G Chronic Hereditary Hemolytic Jaundice, with Report of Eight Cases and Notes on Measurement of Size of Erythrocytes, *Am J M Sc* **187** 191, 1934 (b) Custer, R P Congenital (Familial) and Acquired Hemolytic Jaundice Review of North American Literature for Late 1930 and 1931, *Folia haemat* **48** 137, 1932

differentiated from toxic hepatitis and hemolytic anemia due to various toxins and infections. There has been considerable controversy as to whether there is a syndrome of acquired hemolytic jaundice. It is felt that this disease is in reality an exacerbation of the congenital type<sup>85</sup>

Treatment of this condition with preparations of iron and arsenic vitamins and irradiation of the spleen has proved to be of no value<sup>84a</sup>. The greatest success has been splenectomy<sup>86</sup>. Transfusions have been invaluable before and after surgical intervention, although occasionally transfusion may increase the hemolytic process<sup>87</sup>. The mortality rate reported by various investigators is less than 5 per cent<sup>86e</sup>. Within two weeks after the operation the blood count returns to normal limits<sup>88</sup> and the jaundice disappears<sup>86a</sup>. Examination of a stained blood film reveals persistent microcytosis<sup>86e</sup>. The abnormality of the fragility of the red blood cells also persists<sup>89</sup> with rare exceptions<sup>90</sup>. In the instances in which splenectomy fails, the diagnosis of familial hemolytic jaundice may be questioned<sup>91</sup>.

#### SICKLE CELL ANEMIA

In 1910 James B. Herrick<sup>92</sup> described a new entity characterized by certain clinical manifestations—sickle-shaped erythrocytes in the peripheral blood and severe anemia. Mason<sup>93</sup> in 1922 gave the condition the name sickle cell anemia, which is now generally accepted.

85 Dawson, B. E. Hume Lectures on Haemolytic Icterus. *Brit M J* **1** 921 and 963, 1931.

86 (a) Hargis, E. H., and Simon, H. E. Splenectomy for Hemolytic Jaundice, *South Surgeon* **1** 334, 1933. (b) Livingstone, J. L., and Edwards, H. Acholuric Jaundice Treated by Splenectomy, *Proc Roy Soc Med* **26** 366, 1933. (c) Joyce, J. L., and Mills, J. Three Cases of Familial Acholuric Jaundice, *ibid* **26** 366, 1933. (d) East, T. Acholuric Jaundice with Almost Normal Erythrocyte Fragility, *ibid* **26** 365, 1933. (e) Pemberton, J. deJ. Results of Splenectomy in Splenic Anaemia. Haemolytic Jaundice and Haemorrhagic Purpura, *Tr Am S A* **49** 346, 1931. (f) Thomson, A. P. Acholuric Jaundice with Increased Fragility of Red Blood Corpuscles Appearing After Splenectomy, *Lancet* **2** 1139, 1933. (g) Harris, K. E. Acholuric Jaundice Associated with Purpura, *Proc Roy Soc Med* **26** 369, 1933. (h) Else, J. E. Familial Hemolytic Icterus, *S Clin North America* **13** 19, 1933. (i) Footnote 84.

87 Footnotes 84a and 85.

88 Footnote 86f and g.

89 Footnote 86c and f.

90 Joyce, T. M. Hemolytic Jaundice, *S Clin North America* **13** 77, 1933.

91 Toland, C. G. Fatal Hemolytic Crisis One Year Following Splenectomy for Splenic Anemia, *West J Surg* **41** 91, 1933. Freund, M. Hemolytic Jaundice Not Influenced by Splenectomy, *Am J Dis Child* **43** 645 (March) 1932.

92 Herrick J. B. Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, *Arch Int Med* **6** 517 (Nov 15) 1910.

93 Mason, V. R. Sickle Cell Anemia, *J A M A* **79** 1318 (Oct 14) 1922.

A short time later Sydenstricker<sup>94</sup> and his associates demonstrated that this disease is not uncommon among members of the Negro race. A comprehensive review of the literature up to 1929 has been written by Steinberg<sup>95</sup>

Corrigan and Schiller<sup>96</sup> reported 8 cases of sickle cell anemia and recorded the recognition of the disease in New England for the first time. They emphasized that the disease might masquerade under such diagnoses as rheumatic fever, tuberculosis, acute abdominal conditions, syphilis and obscure forms of anemia. As a relatively high percentage of Negroes have this type of anemia they urged the study of preparations of fresh blood when any of the aforementioned diagnoses are considered in patients of this race. In the case of 1 patient, aged 23, a necropsy was performed, and changes in the spleen and liver and marked hyperplasia of bone marrow were the prominent pathologic observations, the spleen, which weighed 0.87 Gm, is probably the smallest on record. As to treatment, Corrigan and Schuller concluded that a satisfactory form would probably not be developed until the mechanism causing the sickling was discovered. Transfusions of blood had only a temporary beneficial effect. Large doses of preparations of arsenic and iron and a high intake of vitamins are of no special value. One patient was given twenty-two consecutive daily injections of 5 cc of liver extract without any appreciable effect being obtained on the reticulocyte count or the general blood picture. These authors reviewed the effect of splenectomy in patients with this disease who have splenic enlargement and stated that in more than half of them this operation was followed by freedom from symptoms and some improvement in the general blood picture, but the sickle cell trait remained unchanged. Lash<sup>97</sup> reported the case of a Negro primipara, aged 21, in whom death followed a long labor and cesarean section. Although the diagnosis was not made during life, the autopsy observations were characteristic of sickle cell anemia. The patient's spleen weighed 960 Gm, which is the largest reported in the literature. The baby survived, and moist preparations of fresh blood showed sickle cells after twenty-four hours.

Ching and Diggs<sup>98</sup> reported the case of a Negro girl, aged 18 years, with this condition in whom extensive clinical and hematologic studies

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94 Sydenstricker, V. P. Sickle Cell Anemia, *South M. J.* **17** 177, 1924, Further Observations on Sickle Cell Anemia, *J. A. M. A.* **83** 12 (July 5) 1924

95 Steinberg, B. Sickle Cell Anemia, *Arch. Path.* **9** 876 (April) 1930

96 Corrigan, J. C., and Shiller, I. W. Sickle Cell Anemia. Report of Eight Cases, One with Necropsy, *New England J. Med.* **210** 410, 1934

97 Lash, A. F. Sickle Cell Anemia in Pregnancy, *Am. J. Obst. & Gynec.* **27** 79, 1934

98 Ching, R. E., and Diggs, L. W. Splenectomy in Sickle Cell Anemia. Report of a Case with Necropsy in an Adult on Whom Splenectomy Was Attempted, *Arch. Int. Med.* **51** 100 (Jan.) 1933



were made over a period of two years and on whom a complete autopsy was performed. The patient received a transfusion of blood and was given a diet of liver. In addition, she was given sodium cacodylate, dilute hydrochloric acid and mercury and iodide tablets. This was followed by slow improvement. The authors expressed the belief, however, that no conclusions can be drawn as to the effect of liver or other therapy because too many antianemic measures were concurrently employed. A short time later the patient suffered a relapse, and an attempt was made to perform a splenectomy, but the spleen could not be found. This was readily explained at necropsy, for the fibrotic remnant of this organ was flattened out and was so firmly adherent to the diaphragm that it appeared to be a part of it. The authors concluded that the benefits of splenectomy have not yet been proved. If this procedure is to be given a further trial it should be attempted only in cases in which there is splenomegaly. This appears to be a logical statement because the removal of a small spleen may be of no value and in some instances, as in the authors' case, impossible.

Rosenfeld<sup>99</sup> reviewed the literature on sickle cell anemia in the white race. He regarded the report of Cooley and Lee<sup>100</sup> of a case of sickle cell anemia in a white child of Greek descent as the first case in which no reasonable suspicion can be raised of an admixture of Negro blood. The second case, in a white native-born American of Scotch-Irish parentage, reported by Sights and Simon,<sup>101</sup> Rosenfeld did not completely accept because the absence of data concerning the patient's family did not make it possible to exclude definitely the admixture of Negro blood. His own patient came from a family in which three generations had shown the sickling trait and five generations were known to be of the white race from a region where Negroes are practically unknown.

Lawrence,<sup>102</sup> Hunter<sup>103</sup> and others have reported a hereditary deformity of red blood cells occurring in both white persons and Negroes, characterized by elliptic and oval erythrocytes in the peripheral blood of otherwise normal persons. There is no evidence to indicate that this condition is related to sickle cell anemia, but the possibility should be considered.

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99 Rosenfeld, S, and Pincus, J. B. The Occurrence of Sicklemia in the White Race, *Am J M Sc* **184** 674, 1932

100 Cooley, T. B. and Lee, P. Sickle Cell Anemia in a Greek Family, *Am J Dis Child* **38** 103 (July) 1929

101 Sights, W. P., and Simon, S. D. Marked Erythrocytic Sickling in a White Adult, Associated with Anemia, Syphilis and Malaria. Report of a Case, *J Med* **12** 177, 1931

102 Lawrence, J. S. Human Elliptical Erythrocytes, *Am J M Sc* **181** 240, 1931

103 Hunter, W. C. Further Studies of White Family Showing Elliptical Erythrocytes, *Ann Int Med* **6** 775, 1932

## APLASTIC ANEMIA

The literature, consisting mostly of reports of cases, is rather confused, as cases of true aplastic anemia, aleukemic leukemia, pernicious anemia and agranulocytosis are erroneously classified under this heading. Several reports deal with the diagnosis by means of biopsy of bone marrow. Among the etiologic agencies mentioned in the reports were arsphenamine, neoarsphenamine, arsenic, benzene, roentgen rays, sepsis lenta, intestinal stenosis, pregnancy and aleukemic leukemia as well as an idiopathic form.

Various forms have been described. Of the aplastic and hypoplastic myeloses, three groups can be distinguished: (1) partial—(a) erythropenic, (b) leukopenic and (c) thrombopenic, (2) mixed—(a) erythro-leukopenic, (b) erythroid thrombopenic and (c) leukothrombopenic and (3) total—erythroleukothrombopenic.<sup>104</sup>

In an analysis of 13 cases, Thompson, Richter and Edsall<sup>105</sup> found that 12 occurred in men. The age varied from 25 to 70 years (average, 46). The first symptoms were weakness and pallor coming on insidiously and rarely purpuric manifestations. The average red blood cell count remained about 1,500,000 per cubic millimeter, with a hemoglobin content of 20 per cent (Sahli). Severe leukopenia was the rule, and platelets numbered less than 50,000 per cubic millimeter. The reticulocytes varied from 0.1 to 18 per cent. The bone marrow was not always aplastic, however, and hypoplasia or even hyperplasia of the elements was noted.

## ACUTE HEMORRHAGE

Acute massive hemorrhage is primarily a vascular problem.<sup>106</sup> The arterial, venous and capillary blood pressure decreases. The flow of blood decreases, the heart rate increases, an increased amount of epinephrine is discharged into the circulation, the spleen contracts, pouring its stored blood into the general circulation, and local areas of vasoconstriction occur. The respiratory rate increases owing to local asphyxia in the respiratory center and to the lactic acid coming into the circulation from the tissues as tissue fluid enters the capillaries as a result of the fall in capillary blood pressure. Urinary secretion decreases. Adolphe, Gerbası and Lepore<sup>106a</sup> studied the rate of dilution

104 Baserga, A. Le mielosi aplastiche contributo sperimentale ed anatomicopatologico, *Haematologica*, I Arch **13** 481, 1932.

105 Thompson, W. P., Richter, M. N., and Edsall, K. S. An Analysis of So-Called Aplastic Anemia, *Am J M Sc* **187** 77, 1934.

106 (a) Adolphe, E. F., Gerbası, M. J., and Lepore, M. J. Rate of Entrance of Fluid into the Blood in Hemorrhage, *Am J Physiol* **104** 502, 1933. (b) Neumann, B. Experimentelle Beiträge zum Studium des Blutverlustes. II Die Veränderungen der Eiweisswerte und des osmotischen Druckes im Serum und das Auftreten junger Erythrocyten, *Arch f klin Chir* **172** 529, 1932.

of the blood in dogs after a hemorrhage of one third of the blood volume. Dilution was completed in about twenty-two minutes, or at a rate of 0.25 cc per kilogram per minute. Analytic methods for the study of changes in tissue fluids were unsatisfactory. Neumann<sup>106b</sup> stressed the importance of circulatory adjustments and called attention to the character of the fluid which diluted the blood, namely, a fluid low in protein and relatively high in salt.

Studies of changes in the size of the red blood cells following acute hemorrhage have yielded contradictions. Camero and Krumbhaar<sup>107</sup> bled dogs of 60 per cent of the blood volume, and the following day bled them of 30 per cent of the original volume. A definite increase of the mean diameter of the red cells (from 7.6 to 8.3 microns) and of the mean corpuscular volume (from 52 to 87 cubic microns) was observed. Leichsenring and Honig<sup>108</sup> bled dogs of only 25 per cent of the blood volume on two successive days, then of 50 cc weekly, and observed a progressive decrease in both the diameter of the red cells and the mean corpuscular volume during the following six months. Murphy and Fitzhugh<sup>109</sup> reported an increase in the mean corpuscular volume after acute hemorrhage and a decrease after chronic hemorrhage in human beings.

Lindenbaum<sup>110</sup> studied the bone marrow at frequent intervals after a single hemorrhage of two fifths of the blood volume in rabbits. Within the first hour after the hemorrhage there was an increase in the number of mitotic figures in the hemocytoblasts, myelocytes and erythroblasts, which, along with the markedly increased cellularity of the bone marrow, reached a peak on the fourth day after the hemorrhage. The number of megakaryocytes increased in a similar manner. Lindenbaum expressed the belief that posthemorrhagic leukocytosis is due to displacement of these cells by the hyperplasia occurring in the bone marrow. The bone marrow remained hyperplastic after twenty-two days. Lewin<sup>111</sup> confirmed Lindenbaum's observations on the bone

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107 Camero, A. R., and Krumbhaar, E. B. The Effect of Experimental Massive Hemorrhages on the Size of the Red Blood Cell in Dogs, *Am J Physiol* **103** 407, 1933.

108 Leichsenring, J. M., and Honig, H. H. Blood Regeneration Studies. I. Changes in the Volume, Number and Size of the Erythrocytes in Hemorrhagic Anemia, *Am J Physiol* **98** 636, 1931.

109 Murphy, W. P., and Fitzhugh, G. Red Cell Size in Anemia. Its Value in Differential Diagnosis, *Arch Int Med* **46** 440 (Sept.) 1930.

110 Lindenbaum, J. S. Das Knochenmark in den ersten Stunden und Tagen nach dem Aderlass, *Folia haemat* **39** 501, 1930.

111 Lewin, O. Die morphologischen Veränderungen in den blutbildenden Organen nach akuten Blutverlusten. Experimentelle Untersuchungen, *Beitr z path Anat u z allg Path* **88** 394, 1932.

marrow and studied the changes in the liver, spleen and lymph nodes. Associated with hyperplasia of the marrow, Lewin observed proliferation of the reticulo-endothelial system and, contrary to previous studies, myeloid metaplasia of the spleen. In both of these studies fixed tissue sections of the marrow were employed. Using films made of suspensions of bone marrow stained with Wright's stain, Steele<sup>112</sup> studied the ratio of megaloblasts, normoblasts, reticulocytes and mature red cells in the bone marrow of rabbits after acute and chronic hemorrhage and poisoning with phenylhydrazine. On the fifth day following a single hemorrhage of one third of the blood volume the number of normoblasts increased to twice the normal proportion while the percentage of mature red cells decreased a corresponding amount, the number of the other two types of cells remaining unchanged.

Gordon<sup>113</sup> studied litter mate rabbits subjected to the same hemorrhage (one sixty-fourth of the body weight). The red cell count fell to the same minimum level on the day following the bleeding in all the rabbits and returned to the normal level in the same time. The number of reticulocytes reached the peak on the fifth day in all the rabbits and varied individually only between 6.6 per cent and 7.2 per cent.

Eaton and Damren<sup>114</sup> estimated the duration of the existence of the red cell in the circulation at about eight days on the basis of the interval of time between recurring peaks in the reticulocyte count following a hemorrhage and on the basis of a mathematical relationship between two types of reticulocytes.

Miller and Rhoads<sup>115</sup> made an interesting morphologic observation in chronic hemorrhagic anemia. Rabbits were bled continually in sufficient amounts to maintain a 50 per cent hemoglobin level, and the hemoglobin thus removed was reinjected into the same animal subcutaneously. The blood of such rabbits showed a high color index and a mean corpuscular volume above the normal level compared with that of animals which were bled but which did not receive the hemoglobin by injection and in which the color index and mean corpuscular volume were low. At autopsy a megaloblastic marrow was found in the first animals compared with the normoblastic marrow present in

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112 Steele, B. F. The Effects of Blood Loss and Blood Destruction upon Erythroid Cells in the Bone Marrow of Rabbits, *J. Exper. Med.* **57** 881, 1933.

113 Gordon, A. S. The Quantitative Nature of the Red Cell Response to Single Bleeding, *Proc. Soc. Exper. Biol. & Med.* **31** 563, 1934.

114 Eaton, P., and Damren, F. L. A Method for Determining the Life Duration of the Erythrocyte. II. The Rate of Red Cell Production After Hemorrhage, *South. M. J.* **23** 395, 1930.

115 Miller, D. K., and Rhoads, C. P. The Effect of Hemoglobin Injections on Erythropoiesis and Erythrocyte Size in Rabbits Rendered Anemic by Bleeding, *J. Exper. Med.* **59** 333, 1934.

animals subjected to hemorrhage only. A similar predominance of megaloblasts was reported by Steele<sup>112</sup> in rabbits after poisoning with phenylhydrazine.

From the hematologic point of view treatment is seldom necessary after even a moderately acute hemorrhage in an otherwise normal person. Pepper and Farley<sup>116</sup> stated that after the removal of 500 cc of blood from a normal donor of blood all signs of increased regeneration of red cells disappear in one week's time. The reserve stores of the body are adequate to care rapidly for a single moderate loss of blood.

Additional information concerning anemia associated with chronic hemorrhage will be found under the heading "iron deficiency anemia."

#### CANCER

Although anemia<sup>117</sup> is common in association with cancer, it is by no means always present, nor does it necessarily localize the lesion. If the material necessary for the maturation of red blood cells cannot reach the bone marrow macrocytic anemia develops,<sup>118</sup> if there is a disturbance of iron metabolism (failure of absorption or chronic hemorrhage) microcytic anemia appears. Thus, the color index may be high or low. In the majority of instances mild leukocytosis is present. The platelets may be increased, decreased or normal. The treatment of anemia associated with cancer depends on the etiology. The anemia may be aided by antianemic therapy,<sup>119</sup> but it cannot be eliminated without removal of the primary causal factor.

#### INFECTION

The normal blood picture is a reflection of the balance between the production and the destruction of cells. As a result of infection there may be an increased destruction of red blood cells or a decreased production, and hence anemia<sup>120</sup>. As a compensatory measure for the increased demand of red blood cells by the reaction of the body immature

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116 Pepper, O. H. P., and Farley, D. L. *Practical Hematological Diagnosis*, Philadelphia, W. B. Saunders Company, 1933.

117 Morrison, M. *Analysis of Blood Picture in One Hundred Cases of Malignancy*, J. Lab. & Clin. Med. **17** 1071, 1932.

118 Conner, H. M., and Birkeland, I. W. *Coexistence of Pernicious Anemia and Lesions of Gastro-Intestinal Tract. Carcinoma of Stomach, Consideration of Twenty Cases, Eleven Reported*, Ann. Int. Med. **7** 89, 1933. Musser, J. H. *Anemias Simulating Pernicious Anemia*, Proc. Internat. Assemb. Inter-State Post-Grad. M. A. North America **6** 409, 1931.

119 Goldhamer, S. M., and Bethell, F. H. *The Value of Iron Therapy in Secondary Anemia*, to be published.

120 Markowitz, B. *The Hematopoietic System and Infection*, Am. J. Clin. Path. **2** 449, 1932.

red blood cells are released into the peripheral circulation. Many of the young cells are hypochromic, as they have had insufficient time to take up iron.<sup>121</sup> Secondary anemia is thus produced.

In addition to microcytic anemia most infections are characterized by leukocytosis. However, the total number of white blood cells is not as important as the type of leukocyte. The more severe the infection, the more immature are the myeloid cells.<sup>122</sup> As the infection subsides older cells reappear.<sup>123</sup> A useful interpretation of the severity and progress of infection can thus be ascertained. The reappearance of eosinophils is likewise to be interpreted as a favorable sign in a subsiding infection. The secondary anemia and hemogram are of clinical value in determining the presence and course of infection, but they do not aid in localizing the site.

#### ENDOCRINE DISTURBANCES

The coexistence of anemia and myxedema has been observed by a number of investigators. It may be of the primary<sup>124</sup> or of the secondary<sup>125</sup> type and may be related directly to the thyroid dysfunction or may exist as an independent condition. To be on the safe side it is best to treat the two conditions separately.

A specific blood picture related to hyperthyroidism has been reported, however, there appears to be a wide divergence of opinion concerning this. A relative and absolute increase in lymphocytes<sup>126</sup> has been observed in some instances, and in others, a relative and absolute monocytosis,<sup>127</sup>

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121 Kugelmass, I. N., and Lampe, M. Mechanism of Anemia Associated with Infection in Infancy and in Childhood, *Am J Dis Child* **43** 291 (Feb.) 1932.

122 Weiss, A. Blood Picture in Infectious Disease, *J Lab & Clin Med* **16** 655, 1931.

123 Eisenberg, A. A., and Nemans, H. S. Value of Schilling Hemogram in Infections. Preliminary Report Based on Three Thousand Five Hundred Cases, *Am J Surg* **21** 56, 1933.

124 Lisser, H., and Anderson, E. M. Three Cases of Adult Myxedema in Women, Reported for Purpose of Calling Attention to Their Widely Different Symptomatology and Clinical Findings, *Endocrinology* **15** 365, 1931. Davis, C. L. Myxedema with Associated Primary Type of Anemia, *Pennsylvania M J* **34** 873, 1931. Means, J. H., Lerman, J., and Castle, W. B. Coexistence of Myxedema and Pernicious Anemia, *New England J Med* **204** 243, 1931. Kunde, M. M., Green, M. F., and Burns, G. Blood Changes in Experimental Hypo- and Hyperthyroidism (Rabbit), *Am J Physiol* **99** 469, 1932.

125 (a) Lerman, J., and Means, J. H. The Treatment of Anemia of Myxedema, *Endocrinology* **16** 535, 1932. (b) McCullagh, E. P., and Dunlap, J. H. Blood picture in Hyperthyroidism and in Hypothyroidism, *J Lab & Clin Med* **17** 1060, 1932.

126 Gottlieb, R. Blood Studies in Hyperthyroidism, *J Lab & Clin Med* **19** 371, 1934. Footnote 125b.

127 Hertz, S., and Lerman, J. Blood Picture in Exophthalmic Goitre. Changes Resulting from Iodine and Operation, Study by Means of Supravital Technic, *J Clin Investigation* **11** 1179, 1932.

while a third investigator<sup>128</sup> stated that the differential blood picture in hyperthyroidism is normal and hence of no clinical importance from a diagnostic standpoint

#### DISEASES OF THE KIDNEYS

In cases of chronic nephritis 56 per cent of the patients may have anemia (hemoglobin content less than 70 per cent, red blood cells less than 4,000,000 per cubic millimeter) In about 90 per cent of the cases there is a close correlation between the degree of retention of nitrogen and anemia<sup>129</sup> For prognosis, a 40 per cent concentration of hemoglobin has about the same prognostic significance as a blood creatinine value of 5 mg per hundred cubic centimeters or of advanced neuroretinitis<sup>130</sup> Three cases of nephritis have been noted in which anemia was the predominant symptom, without edema or hypertension<sup>131</sup> In cases of acute and chronic glomerular nephritis, essential hypertension (nephrosclerosis), and polycystic kidney and after unilateral nephrectomy the condition of the blood is closely correlated with the degree of impairment of renal function, as measured by Mosenthal's criteria of the volume and specific gravity of the urine during twenty-four hours<sup>132</sup> The anemia may be masked by associated congestive heart failure<sup>131</sup> The degree of anemia is also correlated with the degree of impairment of renal function as measured by the test of urea clearance<sup>133</sup> Retention of nitrogen may occur, however, without anemia<sup>134</sup> The bone marrow may be fatty and relatively aplastic The red blood cells tend to be small, and the color index is about 0.9<sup>135</sup>

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128 Jackson, A. S. Blood Picture in Six Hundred Cases of Goitre, Especial Reference to Effect of Iodine and Thyroidectomy, *J. A. M. A.* **97** 1954 (Dec 26) 1931

129 Brown, G. E., and Roth, G. M. Anemia of Chronic Nephritis, *Arch. Int. Med.* **30** 817 (Dec) 1922

130 (a) Berg, B. N. Blood in Chronic Nephritis Associated with Nitrogen Retention, *Am. J. M. Sc.* **164** 88, 1922 (b) Parsons, L., and Ekola-Strolberg, M. Anemia in Azotemia, *ibid.* **185** 181, 1933 (c) Scarlett, E. P. Significance of High-Grade Anemia in Chronic Nephritis, with Report of Four Cases, *ibid.* **178** 215, 1929

131 Ashe, B. Hemoglobin Percentage and Red Blood Cell Count in Bright's Disease, Myocardial Insufficiency and Hypertension, *Arch. Int. Med.* **44** 506 (Oct) 1929

132 Mosenthal, H. O., and Lewis, D. S. A Comparative Study of Tests for Renal Function, *J. A. M. A.* **67** 933 (Sept 23) 1916

133 Van Slyke, D. D., et al. Observations on Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy, *Medicine* **9** 257, 1930

134 Aubertin, C., and Yacoel, J. L'anémie dans le néphrite azotémique, *Presse méd.* **28** 461, 1920

135 Klemperer, P., and Otani, S. "Malignant Nephrosclerosis" (Fahr), *Arch. Path.* **11** 60 (Jan) 1931 Footnotes 130b and c and 131

The anemia is more common in the nephrotic stage of glomerular nephritis than in lipid nephrosis<sup>136</sup> The associated infection in children may be a factor in producing the anemia<sup>137</sup> The associated conditions, such as epistaxis and gross hematuria, may be contributing factors<sup>138</sup> During the terminal stage there may be mild neutrophilic leukocytosis, occasionally with an increase in the number of eosinophils According to some workers, leukocytosis is present in uremia only if there is associated infection<sup>139</sup> There appears to be no direct correlation between the hemorrhagic diathesis and the number of blood platelets<sup>136</sup>

## EFFECT OF METALS, DRUGS AND RADIATION

### LEAD

The hematologic changes associated with lead poisoning continue to receive considerable attention Punctate basophilia (stippling) of the red blood cells in the peripheral blood stream is, in the absence of marked anemia, good evidence of exposure to lead<sup>140</sup> Badham<sup>141</sup> reported that stippling is usually correlated with excretion of lead Stippling occurs in other disorders of the blood, such as pernicious anemia<sup>140a</sup> It has also been noted as an early sign of benzene poisoning by McCord,<sup>142</sup> and Litzner<sup>143</sup> reported its presence in 8 cases of anemia associated with contracted kidney in the primary or secondary stage with retention of nitrogen in which no exposure to lead had occurred

Several papers have been devoted to the nature of polychromatophilia of the red blood cells and the relationship of diffuse basophilia, punctate basophilia and the reticulum as revealed by supravital staining According to Cooke and Hill,<sup>144</sup> polychromatophilia is due to the presence of the remains of the cytoplasm of the erythroblast, which in the immature red blood cell has not completely disappeared Supravital

136 Wilbur, D L, and Brown, G E Blood in Lipoid Nephrosis, with Special Reference to Absence of Anemia, *Arch Int Med* **45** 611 (April) 1930

137 Clausen, S W Parenchymatous Nephritis as a General Systemic Disorder, *Am J Dis Child* **29** 581 (May) 1925

138 Pákozdy, K Ueber den Zusammenhang zwischen den Nierenkrankheiten und den hamorrhagischen Diathesen, *Ztschr f klin Med* **112** 124, 1929

139 Footnotes 130b, 134, 136 and 137

140 (a) Nelson, W T, Lockwood, L, and Mackay, K The Incidence of Punctate Basophilia, *M J Australia* **2** 317, 1932 (b) Lane, R E Rôle of Punctate Basophilia in the Control of Industrial Plumbism, *J Indust Hyg* **13** 276, 1931

141 Badham, C Basophilia and Lead Excretion in Lead Poisoning, *M J Australia* **2** 816, 1933

142 McCord, C P Industrial (Benzol) Benzene Poisoning Presence of Immature Red Cells in the Blood Stream, *Warthin Anniv Vol* 1927, p 39

143 Litzner, S Ueber das Vorkommen basophil getupfelter roter Blutkörperchen bei Schrumpfnieren, *Med Klin* **29** 81, 1933

144 Cooke, W E, and Hill, C F II Microscopical Studies in Pernicious Anemia, *J Roy Micr Soc* **51** 14, 1931



stains, such as brilliant cresyl blue, act on the surface of the red blood cell in such a way that the stain enters the cell, precipitating this diffuse cytoplasmic material into clumps. Whether the basophilia appears diffuse or punctate depends on the condition of the surface of the red blood cell and on the staining methods<sup>145</sup>. During reticulocytosis following hemorrhage in rabbits Key<sup>146</sup> long ago demonstrated that the stippled cell was a reticulocyte with abnormal staining properties due to the effect of lead. Whitby and Britton<sup>145a</sup> confirmed these observations in a study of the influence of lead during anemia caused by phenylhydrazine. These last two observers, as well as others, have pointed out that the sum of the stippled cells and the diffusely basophilic cells is approximately equal to the reticulocyte count. Accordingly, stippled cells appear to be immature red blood cells the basophilic staining properties of which have been altered by the effect of lead or other agents. Since lead acting in vitro on red blood cells does not cause stippling,<sup>145a</sup> the alteration must occur in the bone marrow. Stippling, however, is not seen in fixed sections of bone marrow<sup>147</sup>. Several observers<sup>148</sup> have reported that the degree of stippling in relation to diffuse basophilia in a blood film depends on the rate of drying of the film and on the stain employed.

The mechanism of the action of lead on the red blood cell was carefully studied by Aub and his associates<sup>149</sup>. They concluded that lead combined in the circulation with the phosphates of the red cell, thus damaging the lipoidal cell membrane and producing a shrunken, brittle and more fragile red blood cell. Maxwell and Bischoff<sup>143b</sup> made a further study of this chemical phenomenon.

Brookfield<sup>145c</sup> in an investigation of the treatment of cancer in human beings and McLean<sup>150</sup> of its value in animals with cancer studied the

145 (a) Whitby, L. E. H., and Britton, C. J. C. The Relation of Stippled Cell and Polychromatic Cell to Reticulocyte, *Lancet* **1** 1173, 1933. (b) Maxwell, L. C., and Bischoff, F. The Reaction of Lead with Constituents of Erythrocyte, *J. Pharmacol. & Exper. Therap.* **37** 413, 1929. (c) Brookfield, R. W. Blood Changes Occurring During Course of Treatment of Malignant Disease by Lead with Special Reference to Punctate Basophilia and the Platelets, *J. Path. & Bact.* **31** 277, 1928.

146 Key, J. A. Lead Studies. III. Blood Changes in Lead Poisoning in Rabbits with Especial Reference to Stippled Cells, *Am. J. Physiol.* **70** 86, 1924.

147 Seifert, G., and Arnold, A. Zell Veranderungen in Knochenmark, Blut und Milz bei experimenteller Bleivergiftung, *Arch. f. Hyg.* **99** 272, 1928.

148 Bruckner, H. Arbeiten uber die basophile Substanz in den jugendlichen roten Blutkorperchen, uber die Wirkung der Fixierung und uber den Einfluss der Wasserstoffionenkonzentration der Farblösungen auf die Darstellbarkeit der basophilen Substanz, *Arch. f. Hyg.* **99** 236, 1928. Footnote 145a.

149 Aub, J. C., and Reznikoff, P. Lead Studies. III. The Effect of Lead on Red Blood Cells, Chemical Explanation of Reaction of Lead with Red Blood Cells, *J. Exper. Med.* **40** 189, 1924.

150 McLean, J. A. Changes in the Blood and Hematopoietic Tissue in Experimental Lead Poisoning, *M. J. Australia* **2** 1, 1930.

effects of Blair Bell's colloidal lead preparations administered parenterally Brookfield observed an anemia, occasionally severe, in most of his patients The red blood cell count fell as much as 1,000,000 per cubic millimeter during the first hour after an injection, and at this time a high degree of poikilocytosis was observed both in fixed films and in the wet preparations A reticulocyte response followed, associated with the presence of a large number of stippled red cells The white blood cells and blood platelets showed no constant change In rabbits McLean found a parallel decrease in red blood cells and hemoglobin and a moderate number of reticulocytes and stippled red cells The cell volume and the blood volume showed a marked decrease Leukocytosis was present during the first few days The neutrophils reached a peak on the first day, and the lymphocytes and monocytes on the second day Myelocytes were numerous during the first two days, while the eosinophils increased on the third day There was a sharp transient increase in blood platelets on the first day after the injection of a colloidal lead preparation The bone marrow at first showed granulocytic hyperplasia Many of the cells contained pyknotic nuclei and other signs of degeneration Later these cells were replaced by an erythroblastic hyperplasia Deposits of hemosiderin were prominent The spleen and lymph nodes in surviving animals were hyperplastic, and in those which died, aplastic Seifeit and Arnold <sup>147</sup> reported similar findings

The increase in the excretion of hematoporphyrin reported in cases of plumbism in human beings was observed experimentally by Liebig <sup>151</sup>

Kasahara and his associates <sup>152</sup> have made interesting studies of lead poisoning arising in infants caused by lead contained in Japanese toilet powders and cosmetics A large amount of lead was found in the milk of the infants' mothers Anemia with stippled cells was present in these children, and toxic granules were observed in the neutrophils <sup>153</sup> Davidson <sup>154</sup> reported cases of lead anemia caused by an excessive amount of lead in the drinking water

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151 Liebig, H Ueber die experimentelle Bleihamatoporphyrin, Arch f exper Path u Pharmakol **125** 16, 1927

152 Kasahara, M, and Nosu, S Studien uber die Bleivergiftung im Sauglings- und Kleinkindesalter I Klinische und experimentelle Untersuchungen uber den Uebergang von Blei in die Milch, Ztschr f Kinderh **55** 577, 1933 Kasahara, M, and Nagahama, M II Die Bleianemie im Sauglings- und fruhen Kindesalter, ibid **55** 583, 1933

153 Kasahara, M, and Nagahama, M Das Auftreten der pathologisch granulierten Leukocyten bei infantiler Bleivergiftung, Folia haemat **53** 37, 1934

154 Davidson, L S P, Fullerton, H W, Rae, H J, and Henderson, A Lead Poisoning in the North-East of Scotland, Lancet **2** 374, 1933 Davidson, L S P Macrocytic Hemolytic Anemia, Quart J Med **1** 543, 1932

The presence of stippled red blood cells associated with mild anemia is presumptive evidence of lead poisoning. Removal from exposure and symptomatic treatment are indicated.

Aluminum exerts an effect similar to that of lead on the red blood cells and organs<sup>155</sup>

#### ARSENIC

Severe blood dyscrasias are among the rare complications of the arsphenamine therapy of syphilis. McCarthy and Wilson<sup>156</sup> reviewed the literature thoroughly in 1932, collecting 79 cases which fall into three groups: (1) those of thrombocytopenia, with or without neutropenia, in which the prognosis is uniformly good, (2) those of granulocytopenia, with four fatalities among 12 cases, and (3) those of aplastic anemia with a mortality of 80 per cent. Concerning the first group, Mu<sup>157</sup> reported a study of the blood platelet count following injections of neoarsphenamine. In 10 patients in whom there was no reaction the blood platelet count decreased to less than one half of the normal number during the first few hours after the injection and returned to a higher than normal level on the following day. The simple purpuric reactions occur typically within a few hours of a treatment, and recovery is rapid. Peripheral destruction of the blood platelets without damage to the hematopoietic organs seems to be the most likely explanation. Since McCarthy and Wilson's article appeared, other cases have been reported<sup>158</sup>. Blood dyscrasia has been noted after all types of arsphen-

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155 Seibert, F. B., and Wells, H. G. The Effect of Aluminum on Mammalian Blood and Tissues, *Arch. Path.* **8** 230 (Aug.) 1929.

156 McCarthy, F. P., and Wilson, R., Jr. The Blood Dyscrasias Following the Arsphenamines, *J. A. M. A.* **99** 1557 (Nov. 5) 1932.

157 Mu, J. W. The Effect of Neoarsphenamine on Number of Blood Platelets, *Proc. Soc. Exper. Biol. & Med.* **26** 407, 1929.

158 (a) Loveman, A. B. Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines, *Ann. Int. Med.* **5** 1238, 1932. (b) Rich, M. L. An Unusual Hematologic Reaction to Neoarsphenamine, *J. A. M. A.* **101** 1223 (Oct. 14) 1933. (c) Stephens, D. J. Aplastic Anemia Following Sulpharsphenamine with Recovery, *Am. J. Syph. & Neurol.* **18** 24, 1934. (d) Knott, F. A. A Case of Toxic (N. A. B.) Aplastic Anemia. Death from Pneumonia When Recovering After Fifty-Two Blood Transfusions, *Guy's Hosp. Rep.* **84** 32, 1934. (e) Kostoulas, A. Hemorragies des muqueuses post- "neo-606" et sulfarsenobenzoliques, *Bull. Soc. franç. de dermat. et syph.* **40** 771, 1933. (f) Chevallier, P., Colin, M., Bernard, J., and Ely, Z. Sur les formules sanguines des syndromes hemorragiques toxiques. A propos de six cas d'hemorragies post-arsenobenzoliques recueillis en un an, *Sarg.* **6** 917, 1932. (g) Preti, L. Anemie aplastica semplice eritro- e plastrinopeniche, *Riforma med.* **49** 199, 1933. (h) Bennett, J. B., and Prichard, J. F. Stomatitis with Aplastic Anemia Occurring During the Treatment of Syphilis with Neoarsphenamine, Case Report, *Texas State J. Med.* **29** 40, 1933. (i) Hawkins, H. F. Acute Aplastic Anemia

amine therapy with or without coincident bismuth or mercury therapy and in all stages of syphilitic infection

Moore and Keidel<sup>159</sup> reported a study of exfoliative dermatitis following the injection of arsphenamine. Among 11 cases leukopenia was noted in 6, neutropenia in 10 and eosinophilia in 9. These changes in the leukocytes were present at the time of the first mild untoward reactions, before the severe disturbances following subsequent injections occurred. These authors advocated an examination of the blood in the presence of the mildest symptoms following injection before continuing arsenical treatment. In nearly all of the cases of blood dyscrasia associated with the injection of arsphenamine reported in the literature adequate premonitory symptoms have been present. If the symptoms had been heeded it might have been possible to avoid subsequent serious results. In some cases reported another type of arsenical preparation has subsequently been well tolerated, but in Grund's case<sup>158</sup> there developed the same hemorrhagic reaction to bismarsen as had previously been given to neoarsphenamine.

At autopsy aplastic bone marrow is usually found, but, as in the case of poisoning created by benzene, regenerating marrow has been observed in a patient dying of some intercurrent toxic infectious process as a result of the poor resistance associated with the neutropenic state<sup>160</sup>.

To the presence of the benzene ring in the arsphenamine molecule has been attributed the cause<sup>161</sup> of blood dyscrasias. The rarity of such reactions detracts from such a theory, and from what is known of the transformation and fate of arsphenamine in the body Voegtlin<sup>162</sup> expressed a doubt that the arsphenamine molecule is broken down to a benzene ring in the body. Because of the tendency of these severe reactions to occur after many injections have been given and often following one of the first few treatments immediately after a rest period in the course of treatment, Moore and Keidel<sup>159</sup> suggested that the bone marrow somehow becomes sensitized to the particular arsenical preparation in use. This remains a speculation. Only 1 case of severe depression of the bone marrow associated with inorganic arsenic poisoning

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with Recovery, *ibid* **28** 822, 1933. (1) Grund, J. L. Purpura Hemorrhagica with Profuse Bleeding from the Mucous Membranes Following the Treatment of Syphilis with Bismarsen, *New England J Med* **211** 443, 1934.

159 Moore, J. E., and Keidel, A. Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis, *Arch Int Med* **27** 716 (June) 1921.

160 Stephens, D. J. Aplastic Anemia Occurring During Treatment of Syphilis with Arsphenamines, *Am J Syph* **15** 333, 1931.

161 Farley, D. L. Depressed Bone Marrow Function from Arsphenamines, Including Type of So-Called Agranulocytosis, *Am J M Sc* **179** 214, 1930.

162 Voegtlin, C. Personal communication quoted by Hamilton<sup>165</sup>.

has been reported,<sup>163</sup> although in 28 cases of inorganic arsenic poisoning caused by arsenic orchard spray left in a cider barrel reported by Lawson, Jackson and Cattnach<sup>164</sup> leukopenia, neutropenia and eosinophilia were noted in the survivors between the fifth and twelfth day following the poisoning

The best treatment is prevention, which is usually possible. Infections must be carefully avoided and combated, and transfusions of blood are recommended to tide the patient over until the function of the bone marrow returns to normal

Arsine, an occasional cause of industrial poisoning, produces rapid and severe anemia as a result of a combination of this substance with the hemoglobin in the red blood cells, leading to rapid hemolysis. Hemolysis is a prominent feature of this condition. Leukocytosis and the presence of immature cells of both the red and the white blood cell series are usually found.<sup>165</sup>

#### BENZENE

In acute benzene poisoning no morphologic changes occur in the blood, although a patient surviving an acute massive exposure may subsequently show the hematologic changes found in chronic poisoning. Hamilton<sup>166</sup> has reviewed the extensive literature concerning the action of benzene on animals and on human beings as a result of occupational exposure and in the treatment of leukemic states. Individual idiosyncrasy plays a large rôle in the response to benzene poisoning, and variations in the size of the dose, the route of absorption and the duration of its action in industrial exposure introduce limitless variables. The extensive experience reported shows that no limited hematologic alteration in man or in animals can be ascribed to the effects of benzene. As with all toxic agents, stimulation and depression are observed depending on the size of the dose and the rate of absorption. This is manifested in the various elements of the blood and of the hematopoietic organs. In the blood an increase in the number of one or more of its elements (red blood cells, white blood cells, platelets) or depression of one or

163 Wheelihan, R. Y. Granulocytic Aplasia of Bone Marrow Following Use of Arsenic, *Am J Dis Child* **35** 1032 (June) 1928

164 Lawson, G. B., Jackson, W. P., and Cattnach, G. S. Arsenic Poisoning, *J. A. M. A.* **85** 24 (July 4) 1925

165 Hamilton, A. Industrial Poisoning in the United States, New York, The Macmillan Company, 1929, (a) p. 220, (b) p. 243 and 272, (c) p. 307, (d) p. 280, (e) p. 420, (f) p. 431, (g) p. 332, (h) p. 357, (i) p. 405, (j) p. 493 (k) Fretwurst, F., Hurwitz, S., and Rosenbaum, R. Zur Frage der Arsenwasserstoffvergiftung mit besonderer Berücksichtigung der Blutveränderungen (nach Tierexperimenten), *Ztschr. f. klin. Med.* **123** 703, 1933

166 Hamilton, A. Benzene (Benzol) Poisoning, *Arch. Path.* **11** 434 (March) and 601 (April) 1931

more of these elements is observed. In the early or mild stage a marked increase in the immaturity of the circulating cells often occurs, followed, after continued influence of the poison, by a marked decrease in the number of these blood cells and by the absence of signs of rapid regeneration. The same situation exists in the hematopoietic organs, varying from hyperplasia to aplasia of one or more of the bone marrow elements as well as of the lymphatic and reticulo-endothelial apparatus. The classic picture of aplastic anemia in chronic industrial benzene poisoning is, perhaps, most common: severe anemia with a normal color index, without an increase in the number of immature red blood cells and, usually, with complete absence of such cells. Leukopenia, neutropenia and thrombocytopenia are usually present. Variation in the severity of these abnormalities is associated with great variation in the clinical picture of aplastic anemia, agranulocytic angina or thrombocytopenia purpura haemorrhagica alone or progressing from simple mild purpura to severe aplastic anemia. The occasional observation of hyperplastic bone marrow at autopsy associated with a premortem aplastic blood picture<sup>167</sup> is not disconcerting in the light of a variety of studies on animals and human beings reported for a variety of aplastic conditions of the blood<sup>168</sup> in which the organism has not survived long enough to benefit by the regeneration occurring in the bone marrow.

Two cases of leukemia have been reported following long mild exposure to benzene,<sup>169</sup> and Lignac<sup>170</sup> observed aleukemic and leukemic lymphoblastomas in mice after benzene poisoning.

Since Hamilton's review in 1930 there have appeared only confirmation and further elucidation of the knowledge of the effect of benzene on the hematopoietic system.<sup>171</sup>

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167 Andersen, D. H. Benzol Poisoning with Hyperplasia of Bone Marrow, *Am J Path* **10** 101, 1934.

168 Footnotes 158c and 167.

169 Delore, P., and Borgomano. Leucémie aigue au cours de l'intoxication benzenique. Sur l'origine toxique de certaines leucémies aigues et leurs relations avec les anémies graves, *J de med de Lyon* **9** 227, 1928. Weil, P. La leucémie post-benzolique, *Bull et mém Soc med d hop de Paris* **48** 193, 1932.

170 Lignac, G. O. E. Die Benzol-leukämie bei Menschen und weissen Mäusen, *Klin Wchnschr* **12** 109, 1933.

171 (a) Osgood, E. E. Action of Benzol, Roentgen-Rays and Radium on Blood and Blood Forming Organs, *Ann Int Med* **6** 711, 1932. (b) Merklen, P., and Israel, L. Intoxication par le benzol: aleucie hemorrhagique, autrement dit "hypoleucie hemorrhagiques avec anémie," *Sang* **8** 700, 1934. Harkins, H. Granulopenia and Agranulocytic Angina, *J A M A* **99** 1132 (Oct 1) 1932. Weiskotten, H. G. The Normal Life Span of the Neutrophil (Amphophil) Leukocyte (Rabbit). Action of Benzol, *Am J Path* **6** 183, 1930. Lemetayer, E. Action du benzene sur les leucocytes, *Recherches experimentales chez de cheval*, *Compt rend Soc de biol* **114** 1284, 1933. Reich, C., and Reich, C. Hematopoietic Response of

In the prevention of severe poisoning in industry neutrophilic leukocytosis<sup>166</sup> and an abnormal number of polychromatophilic red blood cells<sup>142</sup> in the circulation are the signs of the early stimulant phase of benzene poisoning which demand removal from exposure to benzene and correction of the working conditions. Benzene notably requires a long time to develop its full toxic effect, symptoms of severe poisoning often occur several months after exposure has ceased. The treatment is that for all aplastic conditions—symptomatic care and repeated transfusions.

#### GOLD

It is interesting that severe reactions of the types (thrombopenic purpura, granulocytopenia and aplastic anemia) occurring after arsphenamine therapy have also been observed following the injection of gold salts intravenously. Gold salts are little used in this country, but Dameshek<sup>172</sup> reported a case and reviewed the literature, collecting 8 cases, 1 of thrombopenia, 1 of granulocytopenia and 6 of aplastic anemia. Reports of 2 other cases<sup>173</sup> have appeared. Dyscrasia following treatment with gold compounds probably exonerates benzene from any etiologic rôle in the similar reactions to arsphenamine. General care and repeated transfusions are the only treatment available. The prognosis, of course, depends on the severity of the depression of bone marrow.

#### OTHER METALS AND POISONS

Bismuth is in common use in the therapy of syphilis. It is not ordinarily given intravenously and no cases of blood dyscrasia following

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the Rat to Injections of Pentnucleotide, and Its Relation to the Treatment of Agranulocytosis, *Am J M Sc* **187** 71, 1934. Beyer, G. Chronische Benzolvergiftung bei Kaninchen (Beobachtungen am Blutbild), *Ztschr f d ges exper Med* **91** 410, 1933. Schillowa, A. Veränderungen bei chronischer Benzolvergiftung (Experimentelle Untersuchung an Kaninchen), *Folia haemat* **49** 447, 1933. Muller, E. Durch Benzol erzeugte Thrombopenie. Ein Beitrag zur Frage der Benzolschädigungen beim Kaninchen, *Beitr z path Anat u z allg Path* **86** 273, 1931. Thompson, W. P., Richter, M. M., and Edsall, K. S. An Analysis of So-Called Aplastic Anemia, *Am J M Sc* **187** 77, 1934. Dassen, R. Intoxicacion benzolica cronica? Síndrome hemorrágico de la mucosa respiratoria (nariz y bronquios). Anemia aguda post-hemorrágica en un anémico crónico. Aleucia hemorrágica final. Curacion, *Semana méd* **2** 230, 1933.

172 Dameshek, W. Aplastic Anemia Following the Treatment of Lupus Erythematosus with Gold Sodium Thiosulphate, With a Review of the Literature of the Hematological Reactions Following Gold Therapy, *New England J Med* **210** 687, 1934.

173 Jullien, W. Aleucie hemorragique observée au cours d'un traitement par la crisalbine. Evolution favorable, *Bull et mem Soc med d hôp de Paris* **50** 174, 1934. Ameuille, P., Kudelski, C., and Joseph, R. Aleucie hemorragique d'apparition retardée observée au cours d'un traitement par la crisalbine, *ibid* **49** 1428, 1933.

its use have been reported in the literature. The internal use of bismuth subnitrate may lead to methemoglobinemia through reduction of the nitrate to nitrite in the intestine.<sup>174</sup>

Mercury is likewise in common use, but no clear cases of hematopoietic reaction to its use have been reported.<sup>175</sup> Dalla Torre<sup>176</sup> reported a case of severe anemia with signs of regeneration in the peripheral blood which followed intensive treatment with injections of mercury in a syphilitic patient in whom two years previously there had developed a pallor during arsphenamine therapy. This patient also had acute mercurial poisoning with stomatitis and nephritis. In industrial exposure to mercury vapor neurologic and renal manifestations predominate, but mild anemia with a low color index and evidences of regeneration may appear.<sup>165b</sup>

Polycythemia has been produced in rats with cobalt.<sup>177</sup> In rabbits germanium dioxide leads to dehydration which is manifested by loss of weight and an increase in the concentration of the blood.<sup>178</sup> Hamilton reported polycythemia followed by anemia in industrial vanadium poisoning<sup>165c</sup> and leukocytosis during an attack of brass-founder's ague (zinc poisoning).<sup>165d</sup>

No deleterious influence of di-nitrophenol, recently incriminated in agranulocytic angina, was observed in the blood or hematopoietic organs of dogs by Tainter and his associates.<sup>179</sup>

Among reactions to volatile industrial poisons Hamilton reported for methyl alcohol, polycythemia, leukocytosis and lymphopenia,<sup>165e</sup> for ethyl ether in young women, polycythemia and leukocytosis,<sup>165f</sup> for phosgene, an increase in both red and white blood cells followed by anemia,<sup>165g</sup> and for hydrogen sulphide, neutrophilic leukocytosis.<sup>165h</sup> Asphyxia without formation of sulphhemoglobin occurs in acute hydrogen sulphide poisoning.<sup>180</sup>

174 Roe, H. E. Methemoglobinemia Following the Administration of Bismuth Subnitrate. Report of Fatal Case, *J. A. M. A.* **101** 352 (July 29) 1933.

175 Herzog, F., and Roscher, A. Zur Klinik und Pathogenese der Kollargol-intoxikation beim Menschen, *Virchows Arch. f. path. Anat.* **236** 361, 1922.

176 Dalla Torre, G. Anemia grave da intossicazione mercuriale, *Riforma med.* **48** 1926, 1932.

177 Orten, J. M., Underhill, F. A., Mugrage, E. R., and Lewis, R. C. Blood Volume Studies in Cobalt Polycythemia, *J. Biol. Chem.* **99** 457, 1933.

178 Hueper, W. C. The Effect of Overdoses of Germanium Dioxide upon the Blood and Tissues of Rabbits, *Am. J. M. Sc.* **181** 820, 1931.

179 Tainter, M. L., Cutting, W. C., Wood, D. A., and Proescher, F. Di-nitrophenol. Studies of Blood, Urine and Tissues of Dogs on Continued Medication and After Acute Fatal Poisoning, *Arch. Path.* **18** 881 (Dec.) 1934.

180 Harrop, G. A., Jr., and Waterfield, R. L. Sulphemoglobinemia, *J. A. M. A.* **95** 647 (Aug. 30) 1930.



Anemia and relative lymphocytosis supposedly due to exposure to gasoline fumes were reported in chauffeurs by Espeut and Salinger<sup>181</sup> Hemolytic hyperchromic anemia with leukopenia involving both the granular and the lymphatic elements with rapid regeneration was produced in rabbits on inhalation of petroleum benzene by Schustrow and Salistowskaja<sup>182</sup> Hamilton<sup>169a</sup> reported a similar condition in industrial gasoline poisoning

A group of substances act on the blood by converting hemoglobin into methemoglobin The nitroderivatives and aminoderivatives of benzene are prominent members of this group<sup>165j</sup> In the presence of industrial exposure the methemoglobin-containing red cells are destroyed in sufficient numbers to produce hemolytic anemia with marked signs of regeneration In such chronic conditions neutropenia is common Voegtlin and his associates<sup>183</sup> made a careful study of tri-nitrotoluene poisoning in dogs and exposed employees Fragmentation and phagocytosis of the red cells containing modified hemoglobin seemed to be the mechanism of this anemia A majority of the exposed workers were anemic and their blood showed signs of rapid regeneration Nitrites in general<sup>174</sup> and potassium chlorate lead to the formation of methemoglobin Acetanilid, acetphenitidin and similar compounds in the excessive doses taken by addicts cause methemoglobinemia If excessive doses are taken over a long period of time severe anemia with signs of regeneration may develop Large doses, however, do not cause the formation of methemoglobin,<sup>184</sup> excessive continuous use seems necessary<sup>185</sup> and even then severe anemia is rare The relationship to sulphhemoglobinemia remains obscure, for excessive use of acetanilid as often leads to sulphhemoglobinemia as to methemoglobinemia<sup>180</sup> The intestinal tract, liver<sup>186</sup> and spleen seem to play an important role in this condition It is obvious that the usual acid hematin method of estimation of the hemoglobin content gives no idea of the oxygen-carrying power of the blood in these cases<sup>187</sup> Reduction in the red blood cells or alteration in the leukocytes is rarely observed

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181 Espeut, G and Salinger, J Veranderungen des Blutbildes bei Kraftfahrern (Benzolschädigung?), Deutsche med Wchnschr **56** 360, 1930

182 Schustrow, N, and Salistowskaja, E Das Blut bei der Benzimintoxikation Deutsches Arch f klin Med **150** 271, 1926

183 Voegtlin, C, Hooper, C W, and Johnson, J M Tri-Nitro-Toluene Poisoning Its Nature, Diagnosis and Prevention, J Indust Hyg **3** 239, 1921

184 Helms, S T Some Facts Concerning the Pharmacological and Physiological Action of Acetanilide, J Am Pharm A **22** 1093, 1933

185 Fischer, L C Chronic Acetanilide Poisoning, J A M A **100** 736 (March 11) 1933

186 Todd, A T The Relationship of Sulphemoglobinemia to Hepatic Deficiency with Report of a Case, Am J M Sc **171** 635, 1926

187 Dieckmann, W J Methemoglobinemia, Arch Int Med **50** 574 (Oct) 1932

In connection with the excessive use of acetanilid Schilling<sup>188</sup> observed "inner bodies" in the red cells which were thought to be areas of methemoglobin in the cell. These bodies were more numerous following splenectomy. In dogs fed acetanilid these bodies were not demonstrable in the blood unless the spleen was removed. Harrop and Waterfield<sup>189</sup> were likewise unable to produce sulphemoglobin in dogs without splenectomy. Zadek and Burg<sup>189</sup> reported a case similar to Schilling's and also found these bodies in the blood of two persons with ill-defined hematopoietic diseases after splenectomy without addiction to drugs. Pyrodine produced the same appearance<sup>190</sup> in the red cells of rabbits and dogs in vivo associated with hemolytic anemia with hyperplastic bone marrow and in the red cells of dogs and human beings in vitro. Phenylhydrazine depends on this hemolytic action for its therapeutic value in polycythemia<sup>191</sup>.

Normal propyldi-sulphide and related compounds contained in onions<sup>192</sup> are among the most recently studied hemolytic agents.

#### RADIATION

Maitland<sup>193</sup> has summarized his experience with internal radiation by alpha particles. His description of osteitis caused by radiation is of importance hematologically. In the first stage the bone marrow is closely packed with promyelocytes, erythroblasts and hemocytoblasts. Eosinophilic myelocytes are prominent, whereas the neutrophils are scarce. Since the granulocytic cells are formed extravascularly, leukopenia without immature forms develops. In the red cells megaloblasts predominate, and macrocytes enter the general circulation. At this stage the peripheral blood shows hyperchromic anemia, with many immature red cells, leukopenia and neutropenia. There is no icterus, and the number of platelets is normal. In the second stage a patchy inflammatory replacement

188 Schilling, V. Ueber einen als Herzfehler erscheinenden Fall von "Innenkorperanämie" aufgedeckt als chronische Antifebrinvergiftung und Coffeinsucht. *Ztschr f klin Med* **108** 709, 1928.

189 Zadek, I, and Burg, K. Innenkorperanämien, *Folia haemat* **41** 333, 1930.

190 Bratley, F. G., Burroughs, H. H., Hamilton, D. M., and Kern, C. The Effect of Pyrodin Poisoning on Blood and Hemolytopoietic System, with Especial Reference to Formation of Heinz-Ehrlich Bodies in Vivo and Vitro, *Am J M Sc* **182** 597, 1931.

191 Hurwitz, S. H., and Levitin, J. The Value of Phenylhydrazine in the Treatment of Polycythemia Vera, *Am J M Sc* **177** 309, 1929.

192 Gruhzit, O. M. Anemia of Dogs Produced by Feeding of Whole Onions and of Onion Fractions, *Am J M Sc* **181** 812, 1931, Anemia in Dogs Produced by Feeding Disulphide Compounds, *ibid* **181** 815, 1931.

193 Martland, H. S. The Occurrence of Malignancy in Radioactive Persons, General Review of Data Gathered in Study of Radium Dial Pointers, with Special Reference to Occurrence of Osteogenic Sarcoma and Interrelationship of Certain Blood Diseases, *Am J Cancer* **15** 2435, 1931.

fibrosis of the bone marrow occurs which is difficult to distinguish from sarcoma. In these areas eosinophilic myelocytes, lymphocytes and plasma cells predominate. In the third stage the marrow is replaced by a fibrous acellular tissue. Microcytic anemia, without signs of regeneration, and leukopenia probably appear. Leukemia as well as osteogenic sarcoma has several times been observed. This type of industrial poisoning has been eliminated by prohibiting the use of the lips in pointing the brush in the painting of luminous dials. Barker,<sup>194</sup> from measurements of the amount of emanation present in rooms in which dials are painted, calculated that there is no danger of pathologic effects. Other workers have demonstrated the adequacy of present protective measures in handling radioactive materials,<sup>195</sup> in which the penetrating gamma rays are the usual source of danger. Dangerous exposure to radioactive materials was formerly common.<sup>196</sup> Hematologic alterations in miners of radioactive ores have been reported by Woldrich.<sup>197</sup> Fatal absorption of alpha rays from drinking radioactive water has occurred.<sup>198</sup>

The penetrating gamma rays from roentgen rays seldom give rise to occupational disease with the precautions prevalent at present.<sup>199</sup> However, the toxic granules in the leukocytes which appear during the roentgen treatment of leukemia<sup>200</sup> have been reported in the neutrophils of the blood of radiologists.<sup>201</sup> Very small doses of roentgen rays in man or animals lead to transient leukocytosis due to lymphocytosis. Therapeutic doses of roentgen rays may cause a transient increase in the number of neutrophils, but in this case lymphopenia is usually present and neutropenia appears later. During the phase of recovery eosinophilia is common. Often the platelets decrease in number. With large

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194 Barker, H. H. Radon Ingestion and Its Possible Health Dangers, *Am J Roentgenol* **31** 673, 1934

195 Schlundt, H., McGavock, W., Jr., and Brown, M. The Dangers of Refining Radioactive Substances, *J Indust Hyg* **13** 117, 1931. Kaye, G. W. C., Gell, G. E., and Binks, W. Protection of Radium Workers from Gamma Radiation, *Brit J Radiol* **8** 6, 1935

196 Mottram, J. C. Red Cell Blood Content of Those Handling Radium for Therapeutic Purposes, *Arch Radiol & Electroth* **25** 194, 1920. de Laet, M. La pathologie professionnelle due aux corps radioactifs, *Ann de med leg* **8** 443, 1928

197 Woldrich, A. Die Blutveränderungen der Radiumarbeiter Joachimsthal's, *Med Klin* **27** 17, 1931

198 Loeb, L. B. The Nature, Effects and Menace of Radium Poisoning in Water, *Water Works Eng* **87** 217, 1934, *Chem Abstr* **28** 2611, 1934

199 Mottram, J. C. Some Blood Examinations of X-Ray Workers, *Brit J Radiol* **5** 156, 1932

200 Bethell, F. H. The Effect of Irradiation on the White Blood Cells in Chronic Myelogenous Leukemia, *J A M A* **104** 147 (Jan 12) 1935

201 Hirschfeld, H., and Moldawsky, J. Ueber das Vorkommen der sogenannten toxischen (pathologischen) Leukocytengranulation bei Radiologen und radiologischen Hilfskräften, *Klin Wchnschr* **11** 1919, 1932

doses of roentgen rays many degenerated white blood cells are seen in the circulation. No constant effect on the red cells has been observed. In chronic mild exposure to roentgen ray neutropenia, lymphocytosis and eosinophilia are the usual changes.<sup>116</sup> Massive irradiation in animals produces an aplastic bone marrow and aplastic anemia,<sup>202</sup> although Martland expressed the opinion that radiation osteitis in human beings caused by roentgen rays is a different reaction from that produced by the internal action of alpha particles.

The recent use of a thorium dioxide solution intravenously to obtain roentgen visualization of the liver, spleen and other viscera led to a study of the latent effects of this procedure on these organs. Tripoli<sup>203</sup> did not find pathologic changes in any organ with the minimal dose required for visualization in a wide variety of animals. No permanent damage occurred after much larger doses. Lambin,<sup>204</sup> however, using in rabbits about twice the smallest doses employed by Tripoli, after many months observed atrophy of the spleen, periportal fibrosis of the liver and aplasia of the bone marrow with an aplastic blood picture. Pohle and Ritchie<sup>205</sup> have confirmed Lambin's observations, using a smaller dose of thorium dioxide solution.

## INFLUENCE OF IRON

### RÔLE OF IRON IN THERAPY

Iron today occupies a place among that select group of preparations which have stood the test of worth. The modern view of iron in therapy may be said to have had its origin in the attempt to reconcile the experience of countless clinicians in the successful treatment of chlorosis with inorganic iron and the doctrine of Bunge<sup>206</sup> that the metal in such a state could not be absorbed and could not contribute to the manufacture of hemoglobin. Yet Bunge may be considered the father of the present conception of deficiency of iron as a primary cause of anemia. He and Abderhalden<sup>207</sup> were able to show that lactating animals store relatively large quantities of iron during the latter period of gestation and that

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202 Footnotes 171a and 193

203 Tripoli, C J, and von Haam, E. The Effects of Toxic and Non-Toxic Doses of Thorium Dioxide in Various Animals, *Proc Soc Exper Biol & Med* **29** 1053, 1932

204 Lambin, P. Aspects histologiques de la fixation du dioxyde de thorium dans les organes, *Compt rend Soc de biol* **109** 66, 1932

205 Pohle, E A, and Ritchie, G. Histological Studies of Liver, Spleen and Bone Marrow in Rabbits Following the Intravenous Injection of Thorium Dioxide, *Am J Roentgenol* **31** 512, 1934

206 Bunge, G. *Lehrbuch der physiologischen und pathologischen Chemie*, ed 4, Leipzig, F C W Vogel, 1898

207 Abderhalden, E. *Ztschr f phys Chem* **26** 498, 1899

this reserve supply is gradually depleted during lactation, which, if unduly prolonged, results in anemia. Whereas men came readily to disbelieve Bunge's view that inorganic iron was unabsorbable, on the other hand, his contention that such iron could take no part in the building of hemoglobin left its mark for many years, both on clinical teaching and on scientific investigation. Thus, in 1920 Nageli<sup>208</sup> wrote that in his opinion chlorosis was due to a sluggishness of the hematopoietic process rather than to a lack of iron and that the benefits of the metal in medicinal form were due to its irritant and stimulative effect either directly on the bone marrow or through an indirect action. This conception of the stimulative effect of iron in medicinal form in the absence of its actual requirement for the formation of blood has by no means disappeared from present-day medical thought, and, as we shall point out later, has been utilized recently by Josephs in his explanation of the effect of iron on a certain type of anemia of infants. Among those who disagreed with the views of Nageli was the French clinician Richaud,<sup>209</sup> who believed that inorganic iron was actually used for the synthesis of hemoglobin when administered in the treatment of chlorosis. He recognized two types of iron deficiency anemia: the first, the result of a dietary lack of the element, and the second, the result of impairment of absorption and utilization of the iron in food. In the latter group he placed chlorosis.

The skepticism toward the efficacy of iron in medicinal form which developed during the first and second decades of the present century and continued until a comparatively recent date was no doubt due to three contributing factors. The first was the gradual disappearance of chlorosis, the disease par excellence which yielded to iron therapy. The second was the use of iron in the treatment of a great variety of conditions, such as pernicious anemia and leukemia, in which it was of no possible benefit. The third, and of great importance, was the practice of administering iron in comparatively minute doses. It was felt, following the teaching of Bunge and Abderhalden, that since inorganic iron could take no part in the formation of blood the metal should be given either in complex organic form or in very small doses for its indirect or stimulating effect. In the past century iron was given in much larger amounts, and no doubt there were some clinicians who never adopted the fashion of minute dosage. To whom to give credit for priority in the restoration of iron to its proper place in therapeutics is impossible to determine. Arneth<sup>210</sup> in 1925 recalled that he had advocated large doses of reduced iron (from 0.75 to 0.9 Gm daily)

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208 Nageli, O. Zur Frage der Eisenwirkung bei Anämien, speziell bei Chlorose, Schweiz med Wchnschr 50 661, 1920

209 Richaud, A. La question du fer medicamenteux, Paris med 10 268, 1920

210 Arneth. Zur Eisentherapie, Deutsche med Wchnschr 51 1115, 1925

twenty years before and that his views are contained in his textbook published in 1907 Alder<sup>211</sup> reported the treatment of a number of patients with chlorosis with reduced iron in pills containing 0.1 Gm, of which he gave from three to ten daily, depending on the severity of the anemia. He believed that the iron acted as an irritant on the blood-forming organs. Lindberg<sup>212</sup> was apparently the first to use reduced iron in really large doses. He administered 1 Gm three times a day with excellent results, to four groups: (1) patients with anemia following influenza (epidemic of 1917-1918), (2) patients with anemias of the puerperium, (3) patients with "benign anemia of unknown origin," and (4) patients with chlorosis. He found no instances of gastrointestinal intolerance to this dosage.

Probably of greatest influence on present practice were the contributions of Meulengracht<sup>213</sup> and Barkan<sup>214</sup>. The former used, among other preparations, reduced iron (from 0.5 to 1 Gm three times a day) in the successful treatment of anemia of chronic hemorrhage, simple anemia associated with achylia gastrica and chlorosis. He found large doses especially beneficial in diseases of the two latter groups. He noted that iron was ineffective in the treatment of anemia associated with infection, nephritis and malignant processes and was useless after acute hemorrhage because of the tendency toward spontaneous regeneration of the blood. Barkan treated patients with typical chlorosis with reduced iron (from 1 to 3 Gm daily). He believed that the iron was converted to ferric chloride by the gastric hydrochloric acid and that the astringent action of the salt irritated the intestinal mucosa and so led to absorption. With the cure of anemia, according to him, the intestine became less susceptible to irritation, and consequently no cumulative absorption of iron with possible toxic effects occurred.

Recognition of the probable influence of the gastric acidity on the absorption of reduced iron led to investigations of the relative availability of bivalent and trivalent iron compounds. Heubner<sup>215</sup> reported that he detected no evidence of absorption of ferric iron from the gastrointestinal tract of dogs, the ferrous form alone being absorbed. Later<sup>216</sup>

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211 Alder, A. Zur Dosierung des Eisens, die Vorzüge hoher Dosen, Schweiz med Wchnschr **50** 663, 1920.

212 Lindberg, G. Ueber Anämie nach Influenza, nebst einigen Bemerkungen zur Eisentherapie der Anämien, Acta med Scandinav **56** 162, 1922.

213 Meulengracht, E. Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, Acta med Scandinav **58** 594, 1923.

214 Barkan, G. Therapie der Anämien mit grossen Eisengaben, Klin Wchnschr **2** 1748, 1923.

215 Heubner, W. Bemerkung zur Eisentherapie, Ztschr f klin Med **100** 675, 1924.

216 Heubner, W. Ueber "organische" Eisenpräparate, Klin Wchnschr **5** 588, 1926.

he investigated various preparations of organic iron. The nature of the organic radicle he found to be of little importance, protein derivatives being unnecessary. Of much greater significance was the valence of the iron, since only ferrous compounds were absorbed. Wiechowski<sup>217</sup> also concluded on the basis of experimental work that ferrous compounds alone were efficacious. Medicinal preparations, he warned, should be scrutinized carefully for possible oxidation to the trivalent form. He found little justification for parenteral administration of iron, as the ferrous preparations for use by mouth are so readily available. He advocated the use of reduced iron since the excess of the metal prevented oxidation by the gastric hydrochloric acid beyond the bivalent stage. Posener,<sup>218</sup> similarly influenced by the work of Heubner, concluded that reduced iron was of no benefit in the treatment of anemia associated with gastric anacidity. He believed that all organic preparations before absorption must be converted to ferrous chloride, and he stated that of available commercial preparations at least 90 per cent were either useless or superfluous. Deserving of special attention at this point are the work and views of Starkenstein. He grouped preparations of iron into four classes:<sup>219</sup> (1) true organic and inorganic acid iron salts (ferrous), which alone of the iron cations exhibits a pharmacodynamic effect, (2) complex compounds of the type of citric, malic and acetic acid combined with iron, which likewise have a strong pharmacodynamic effect, due, however, not to the action of iron cations but to the iron acting as an anion, (3) ferric salts, including ferric hydroxide, which, so far as their action depends on absorption from the gastro-intestinal tract, are entirely ineffective and (4) organic iron-containing compounds of the type of hemoglobin and the ferrocyanides, which also possess no pharmacodynamic effect. For therapeutic purposes, according to Starkenstein, only those preparations of iron should be employed which either are ferrous compounds or become so in the stomach. Compounds of which the iron tends spontaneously to assume the ferric form should be avoided. The medicinal form of choice, he said,<sup>220</sup> is ferrous chloride (free from trivalent iron). He recommended its use in place of reduced iron because its absorption is not dependent on the gastric acidity, because the digestive process in the stomach is not deprived of hydrochloric acid, which is the case when acid is required for chemical inter-

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217 Wiechowski, W. Die Eisentherapie im Lichte der neueren Forschung, *Med Klin* **23** 1765, 1927

218 Posener, K. Ueber die theoretischen Grundlagen der Eisentherapie, *Therap d Gegenw* **68** 541, 1927

219 Starkenstein, E. Die derzeitigen pharmakologischen Grundlagen einer rationellen Eisentherapie, *Klin Wchnschr* **7** 217 and 267, 1928

220 Starkenstein, E. Therapeutischer Wert und chemische Wertigkeit der Eisenpräparate, *Therap d Gegenw* **69** 394 and 451, 1928

action with reduced iron and, finally, because small doses of ferrous chloride are always as effective as the largest doses of reduced iron, even when the latter is given to persons secreting an abundance of hydrochloric acid. To iron as a medicine Starkenstein<sup>221</sup> attributed three functions: (1) a catalyst for respiration of tissue through its presence in cytochrome, (2) a building stone for hemoglobin, and (3) a stimulant to the blood-forming organs. He pointed out that in many cases of apparent deficiency of iron the administration of a preparation of the metal is without effect since the real fault may be either an endocrine disorder or avitaminosis.

To Starkenstein and Heubner is due credit for a great forward step in the still meager knowledge of the processes involved in the assimilation and utilization of iron. Moreover, by their emphasis on the value of ferrous compounds they have made an important contribution to the rational therapy of anemia. It is now agreed by most observers, including Reimann in Germany, Davidson and Witts in Great Britain and Minot in the United States, that in terms of quantity administered simple ferrous compounds, such as the chloride, carbonate and sulphate, are the most effective forms of medicinal iron. However, to regard trivalent iron as totally inactive would require denial of the testimony of clinicians and investigators too numerous to mention. We shall refer only to the observations of Meulengracht,<sup>213</sup> who obtained equally good results with either colloidal ferric hydroxide or reduced iron, and to those of Mitchell and Vaughn,<sup>222</sup> who in treating the milk anemia of the albino rat found that ferric compounds were more efficacious than the bivalent form of iron. The poor showing of the ferrous salts in the latter authors' experiments was probably due to their comparative freedom from copper contamination.

#### THE IRON DEFICIENCY ANEMIAS

From the primary consideration of iron as a therapeutic agent we transfer attention to those conditions in which its use may be attended with benefit. It is customary to group such conditions under the general classification of iron deficiency, although so far as anemia in human beings is concerned such a designation is no more than an assumption, albeit a logical one. Aside from that due to chronic or recurrent bleeding, the iron deficiency anemias are linked definitely to age and sex. They tend to occur in infancy, in the female sex at puberty, in connection with pregnancy and throughout middle life in association with secretory dysfunction of the stomach.

<sup>221</sup> Starkenstein, E. *Neue pharmakologische Richtlinien für die Eisentherapie*, Med Klin **23** 111, 1927.

<sup>222</sup> Mitchell, H. S., and Vaughn, M. *Relation of Inorganic Iron to Nutritional Anemia*, J Biol Chem **75** 123, 1927.



## ANEMIA DUE TO CHRONIC HEMORRHAGE

In temperate climates the most common of all cases of anemia of adults are those due wholly or in part to an abnormal loss of blood, and the majority of these are caused by uterine hemorrhage, bleeding hemorrhoids and bleeding peptic ulcer. Such conditions should offer no great difficulty in diagnosis. During recent years attention has been given to another source of bleeding which may easily be overlooked. We refer to diaphragmatic hernia of the stomach. Moller<sup>223</sup> pointed out the common occurrence of anemia in this condition, and Segal<sup>224</sup> reported 5 cases of diaphragmatic hernia in which no symptoms were present except those attributable to anemia. He suggested as causes of bleeding passive congestion of the herniated portion of the stomach as the result of angulation of veins or pressure on them, ulcer due to varicosities from congestion or disturbed arterial supply. Bock, Dulin and Brooke<sup>225</sup> reported 10 cases of the same condition with surgical notes on 2 and an autopsy diagnosis on 3 others. In their cases the cause of bleeding was said to be congestion of the mucosa of the stomach caused, presumably, by increased venous pressure. Gardner<sup>226</sup> compiled from the literature 22 cases of diaphragmatic hernia with anemia and added 5 others.

A source of incalculable human misery and economic loss is anemia associated with hookworm infestation. It has been variously attributed to toxins produced by the parasite, to derangement of nutrition and to the loss of blood. Suarez<sup>227</sup> in an extensive study of 22 cases of uncinariasis found no interrelation of the hemoglobin content, the number of parasites and the nature of the gastric secretion. He expressed the belief that nutritional factors rather than hemorrhage are of primary importance in causing the anemia. Biggam and Ghaloungui,<sup>228</sup> among others, cured ancylostoma anemia by the administration of iron without preliminary removal of the parasites. Elimination of the worms with-

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223 Moller, F. Zwerchfellhernie und Magenkarzinom. Zugleich einige Betrachtungen über Blutungen und Anämien bei Zwerchfellhernien, *Acta med Scandinav* **74** 421, 1931.

224 Segal, H. L. Secondary Anemia Associated with Diaphragmatic Hernia, *New York State J. Med* **31** 692, 1931.

225 Bock, A. V., Dulin, J. W., and Brooke, P. A. Diaphragmatic Hernia and Secondary Anemia, Ten Cases, *New England J. Med* **209** 615, 1933.

226 Gardner, K. D. Diaphragmatic Hernia Associated with Secondary Anemia, *Am J M Sc* **185** 561, 1933.

227 Suarez, R. M. Clinical Aspects of Uncinariasis, *Puerto Rico J. Pub Health & Trop Med* **8** 229, 1933.

228 Biggam, A. G., and Ghaloungui, P. Ancylostoma Anemia and Its Treatment by Iron, *Lancet* **2** 299, 1934.

out further treatment failed to influence the blood values within a reasonable time. Most favorable results in their series of cases were obtained by the use of reduced iron in doses of 2 Gm three times a day. A definitely slower response was obtained in patients with gastric anacidity. Recovery from anemia was markedly retarded by the administration of reduced iron in smaller quantities, and very little improvement followed the use of ferrous chloride in a dosage of 0.3 Gm daily. In the treatment of hookworm anemia they found liver, brewer's yeast and desiccated thyroid to be of no value, and they detected no appreciable effect from the use of copper or manganese as adjuncts to iron. They regarded parenteral therapy with ferric ammonium citrate (0.1 Gm daily) as generally unsatisfactory, although definitely better results were obtained from intramuscular than from intravenous administration. Observations made on dogs artificially infected with *Ancylostoma caninum* led Foster and Landsberg<sup>229</sup> to ascribe the anemia solely to the effect of loss of blood. They were able to "parallel in every detail the picture of a developing hookworm anemia, including its response to iron therapy, by periodic artificially produced hemorrhage." The extensive investigations of Rhoads, Castle, Payne and Lawson<sup>230</sup> led them to believe that hookworm anemia is due primarily to hemorrhage, which is the sole effect of the parasites per se on the blood, but that a secondary and important rôle is played by dietary deficiency and the gastro-intestinal changes resulting from defective nutrition. They found the anemia characterized by hypochromia and microcytosis with increased cellularity of the bone marrow. Excellent therapeutic results were obtained by the use of ferric ammonium citrate (6 Gm daily) regardless of the nature of the diet. They suggested that to patients with hookworm infestation without anemia small doses of iron should be given as a prophylactic measure.

To the extensive researches of Whipple, Robscheit-Robbins and their collaborators is due much of the knowledge concerning the effects of prolonged or recurrent hemorrhage in depleting not only the body's iron reserves but other materials required for the synthesis of hemoglobin and the formation of erythrocytes. The Nobel prize lecture of Whipple<sup>231</sup> provides so excellent a summary of their work that no extensive recapitulation seems indicated here. Whipple, Hooper and

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229 Foster, A. O., and Landsberg, J. W. Nature and Cause of Hookworm Anemia, *Am J Hyg* **20** 259, 1934.

230 Rhoads, C. P., Castle, W. B., Payne, G. C., and Lawson, H. A. Observations on Etiology and Treatment of Anemia Associated with Hookworm Infestation in Puerto Rico, *Medicine* **13** 317, 1934.

231 Whipple, G. H. Hemoglobin Regeneration as Influenced by Diet and Other Factors, *J. A. M. A.* **104** 791 (March 9) 1935.

Robscheit <sup>232</sup> in 1920 reported the favorable influence of liver on the regeneration of blood in dogs after rapid production of anemia by one or more severe hemorrhages. In 1925 Robscheit-Robbins and Whipple <sup>233</sup> demonstrated the preeminence of liver in terms of the quantitative production of hemoglobin by dogs maintained at a constant level of anemia through repeated removal of small quantities of blood. The results received wide clinical application. With the exception of pernicious anemia, in which the action of liver is that of a specific, there is no unanimity of opinion with regard to the efficacy of liver in the treatment of anemia in human beings. As might be expected, however, its use together with iron has been found of greater value in the management of anemia due to chronic hemorrhage than of others of the iron deficiency group. Keefer and Yang <sup>234</sup> are among the strongest advocates of liver therapy, having found it of greatest benefit in anemia due to chronic hemorrhage, hookworm infestation and faulty diet. Murphy and Powers <sup>235</sup> have reported the value of liver with iron in the treatment of anemia due to hemorrhage, and Dyke <sup>236</sup> and Wahlberg <sup>237</sup> have obtained reticulocyte responses during treatment with liver alone for this type of anemia.

#### DEFICIENCY ANEMIAS OF INFANCY

Bunge <sup>206</sup> found the mineral contents of human milk and of newborn infants to be quantitatively similar with the exception of iron, in which milk proved to be notably deficient. Consequently, he felt that a prolonged milk diet led to iron deficiency and so caused anemia.

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232 Whipple, G. H., Hooper, C. W., and Robscheit, F. S. Blood Regeneration Following Simple Anemia. I. Mixed Diet Reaction, *Am J Physiol* **53** 151, 1920, Blood Regeneration Following Simple Anemia. IV. Influence of Meat, Liver and Various Extractives, Alone or Combined with Standard Diets, *ibid* **53** 236, 1920.

233 Robscheit-Robbins, F. S., and Whipple, G. H. Blood Regeneration in Severe Anemia. Favorable Influence of Liver, Heart and Skeletal Muscle in Diet, *Am J Physiol* **72** 408, 1925.

234 Keefer, C. S., and Yang, C. S. Value of Liver and Iron Treatment of Secondary Anemia, *J A M A* **93** 575 (Aug 24) 1929. Yang, C. S., and Keefer, C. S. Response of the Reticulocytes in Secondary Anemias Following Various Forms of Treatment, *Arch Int Med* **45** 456 (March) 1930. Keefer, C. S., and Yang, C. S. Treatment for Secondary Anemia. Study of Results in One Hundred and Twenty-Six Cases, *ibid* **48** 537 (Oct) 1931.

235 Murphy, W. P., and Powers, J. H. Value of Liver in Treatment of Anemia Due to Hemorrhage, *Surg, Gynec & Obst* **48** 480, 1929. Powers, J. H., and Murphy, W. P. Treatment of Secondary Anemia. Further Observations, *J A M A* **96** 504 (Feb 14) 1931.

236 Dyke, S. C. Liver Therapy in Secondary Anemia, *Lancet* **1** 1192, 1929.

237 Wahlberg, J. Liver Diet and Reticulocyte Reaction in Simple Anemia, *Acta med Scandinav* **72** 143, 1929.

Hugounenq<sup>238</sup> in 1899 analyzed the ash obtained from incineration of fetuses secured at different periods of gestation. He demonstrated that during the last trimester of pregnancy twice as much iron is stored as is laid down during the preceding six months. In 1917 Lichtenstein<sup>239</sup> recorded the observations and drew the conclusions which today form the basis of the knowledge concerning the commoner type of anemia of infants. Hemoglobin and erythrocyte values in the majority of new-born premature babies he found to agree with those obtained from full-term infants. The stained films of the blood of the former, however, revealed a greater incidence of fetal characteristics. Uniformly, he reported, during the first two months of life there develops in the premature infant an anemia characterized by reduction of both the erythrocyte count and the hemoglobin value. This anemia he called hypoplastic, believing it to be due to the partial failure of the immature blood-forming organs to meet the demands imposed by extra-uterine life. During the second quarter of the first year he found that the erythrocyte count of the premature infant increased, whereas the hemoglobin content remained at a low level. This deficiency in hemoglobin he attributed to an insufficient congenital supply of iron together with a milk diet furnishing inadequate amounts of the metal. Thus, the condition was regarded, at least in part, as an alimentary anemia. The failure of others to obtain results from iron in the treatment of this type of anemia Lichtenstein attributed to the use of too small doses. His patients, treated successfully, were given metallic iron (0.15 Gm daily) in powdered form mixed with cane sugar.

The recognition of the bearing of nutrition on anemia in infancy and childhood stimulated investigations of the requirement of iron by normal children. Lichtenstein<sup>240</sup> studied during short periods the intake and excretion of iron in premature infants and found a slight positive balance to be the rule. Rose, Vahlteich, Robb and Bloomfield<sup>241</sup> for nine days carried out a careful study of the iron metabolism in a girl 2½ years of age. The average daily intake of iron was 4.64 mg and the daily output, 5.74 mg, yielding a negative balance of 1.1 mg. For children between 2 and 3 years these investigators advised an iron intake of at least 0.75 mg for each hundred calories furnished by the diet.

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238 Hugounenq, M. L. Recherches sur la statique des éléments minéraux et particulièrement du fer chez le fœtus humain, *Compt rend Soc de biol* **51** 337, 1899.

239 Lichtenstein, A. Hematological Studies of Premature Babies During Infancy with Particular Reference to Anemic Conditions, *Svenska lak-sällsk handl* **43** 1533, 1917, abstr, *Arch Pediat* **43** 738, 1926.

240 Lichtenstein, A. Der Eisenumsatz bei Frühgebornenen, *Acta pædiat* **1** 194, 1921.

241 Rose, M. S., Vahlteich, E. M., Robb, E. and Bloomfield, E. M. Iron Requirement in Early Childhood, *J Nutrition* **3** 229, 1930.

Wallgren <sup>242</sup> conducted twenty-one studies of the iron balance on 5 nursing infants between 3 weeks and 11 months of age. The duration of each experiment was from seven to ten days. All but 4 showed a slight positive balance. Wallgren concluded that in milk contains as little iron as 0.0642 mg per hundred cubic centimeters there is still a sufficient supply to meet the external requirements of the healthy nursing infant, as some dependence may be placed on the iron stores present at birth. Snelling <sup>243</sup> performed twelve experiments on balance, lasting from three to six days, on 7 premature infants. The excretion of pigment was also recorded. Tests on 9 infants on a milk diet revealed a positive balance, and 3 gave a slight negative value. Snelling failed to find excessive excretion of pigment and he believed that the anemia, characterized by equivalent reduction of values for both erythrocytes and hemoglobin, was due to failure to utilize available materials rather than to an increased destruction of blood or to a lack of substances required for the composition of hemoglobin. He suggested that this imperfect utilization was "due to inadequate medullary space coincident with the premature cessation of hematopoietic activity in the liver." Josephs <sup>244</sup> conducted studies of balance of iron from two to six months' duration on 6 normal full-term infants. During the first two months a slightly negative balance occurred, followed by a fairly constant positive balance with an average gain of 6 mg of iron each month. He concluded that the birth stores of iron are required but rarely for the formation of hemoglobin before the third month, and that under normal conditions they are probably sufficient for this purpose until the end of the sixth month. He stated that a diet exclusively of milk cannot cause any great degree of anemia solely on the basis of its low iron content but that in the production of such anemia other factors causing a disturbance of iron metabolism must play a part. Josephs <sup>245</sup> also studied the blood and the excretion of urobilin of a large group of premature infants. During the first six to eight weeks there was a progressive fall in the blood count, the color index remained high, and the rate of destruction of blood exceeded the rate of growth. In this period there was some, but little, excretion of body iron (negative balance). The greater part of the iron released by the breakdown of hemoglobin was available for new blood, and in premature infants, according to

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242 Wallgren, A. Le fer dans la nutrition de l'enfant. III. Recherches sur le métabolisme du fer chez les enfants nourris au sein pendant la première année de leur existence, *Rev. franç. de pédiat.* **9** 196, 1933.

243 Snelling, C. E. Metabolism of Iron in Anemia of Premature Infants, *J. Pediat.* **2** 546, 1933.

244 Josephs, H. W. Iron Metabolism in Infancy. Relation to Nutritional Anemia, *Bull. Johns Hopkins Hosp.* **55** 259, 1934.

245 Josephs, H. W. Anemia of Prematurity, *Am. J. Dis. Child.* **48** 1237 (Dec.) 1934.

Josephs, a true iron deficiency or hypochromic anemia does not occur before the fourth or fifth month. Between the sixth to tenth week and the fourth to fifth month a period of hypoplastic anemia is evident in the sense that the blood count continues to fall, with the color index remaining high, but the bone marrow is reactive and a reticulocyte response will follow the administration of either iron or liver. "They act as stimulators of hemopoietic activity." During the subsequent "hypochromic period" iron serves as a building material for hemoglobin, whereas liver, as a rule, is ineffective for this purpose.

For important contributions both to the understanding of iron metabolism and to the therapy of certain types of nutritional anemia workers are indebted to the Wisconsin investigators Hart, Steenbock, Waddell and Elvehjem<sup>246</sup>. They demonstrated that the anemia induced in growing rats by feeding an exclusive milk diet could not be cured by the administration of pure iron salts but that the availability of iron for the formation of hemoglobin depended on the presence of small amounts of copper. Myers and Beard<sup>247</sup> denied the specificity of copper for this purpose and claimed a similar "biological catalytic" action for numerous other metals. Drabkin and Miller<sup>248</sup> found the amino-acids glutamic acid and arginine useful as adjuncts to iron in the treatment of the nutritional anemia of the growing rat. However, it is generally felt that these apparently conflicting results were due to undetected quantities of copper present either in the diet or in the therapeutic agents employed. The unique rôle of copper as an "activator" of iron has been confirmed by numerous investigators including ourselves.

The addition of copper to therapeutic preparations of iron has failed to produce striking results in the treatment of most types of human anemia. Josephs,<sup>249</sup> Lewis<sup>250</sup> and Bloxson,<sup>251</sup> among others, have found copper a useful adjunct to iron in the treatment of hypochromic anemia of infancy and early childhood, and it appears that copper may achieve a definite place in the therapy of such anemia. Recently Daniels and

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246 Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A. Iron in Nutrition. Copper as Supplement to Iron for Hemoglobin Building in Rat, *J. Biol. Chem.* **77** 797, 1928.

247 Myers, V. C. and Beard, H. H. Studies in the Nutritional Anemia of the Rat. Influence of Iron Plus Supplements of Other Inorganic Elements upon Blood Regeneration, *J. Biol. Chem.* **94** 89, 1931.

248 Drabkin, D. L., and Miller, H. K. Hemoglobin Production. Relief of Anemia Due to Milk Diet by Feeding Amino-Acids, *J. Biol. Chem.* **90** 531, 1931.

249 Josephs, H. Treatment of Anemia of Infancy with Iron and Copper, *Bull. Johns Hopkins Hosp.* **49** 246, 1931.

250 Lewis, M. S. Iron and Copper in the Treatment of Anemia in Children, *J. A. M. A.* **96** 1135 (April 4) 1931.

251 Bloxson, A. P. Copper and Iron Requirements in Infancy, *South. M. J.* **25** 401, 1932.

Wright<sup>252</sup> reported the results of fifteen studies of the iron and copper balance made on 8 normal children from 4 to 6 years of age. They found an average daily retention of iron of 0.18 mg per kilogram of body weight and concluded that a diet furnishing 0.6 mg per kilogram meets the requirements of iron for the maintenance and growth of normal children of the ages studied. The average daily retention of copper from a diet supplying 0.086 mg per kilogram of body weight was 0.026 mg per kilogram. The investigators found higher values for retention of copper when greater quantities were ingested and so recommended that the daily diet supply a minimum of 0.1 mg of copper per kilogram of body weight. It is probable that studies of the requirements of iron and copper in food will have to be reevaluated in the light of recent work on the availability for absorption of the iron and copper contained in various foods.<sup>253</sup>

That the subject of iron deficiency and nutritional anemia in childhood is worthy of the attention accorded it in this review is attested by the work of Mackay<sup>254</sup> in England. In the poorer classes of London she found anemia present in the great majority of artificially fed babies. This she considered to be due primarily to a lack of iron, since the administration of a preparation of the metal to these infants was followed by an increase of the hemoglobin content in 81 per cent. She discovered no relationship between this type of anemia and vitamin deficiency, lack of sunlight or fat toxemia. Ferric ammonium citrate, from 0.3 to 0.6 Gm daily, mixed with dried milk was used in the treatment of her patients. Parsons and Hawksley<sup>255</sup> obtained a more rapid increase in the hemoglobin content following the administration of 0.8 Gm of ferrous sulphate daily. Neither they nor Mackay<sup>256</sup> were able to demonstrate the value of adding copper to purified preparations of iron in the treatment of nutritional anemia of infancy. Recently,

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252 Daniels, A. L., and Wright, O. E. Iron and Copper Retentions in Young Children, *J. Nutrition* **8** 125, 1934.

253 Sherman, W. C., Elvehjem, C. A., and Hart, E. B. Further Studies on the Availability of Iron in Biological Materials, *J. Biol. Chem.* **107** 383, 1934. Schultze, M. O., Elvehjem, C. A., and Hart, E. B. Availability of Copper in Various Compounds as Supplement to Iron in Hemoglobin Formation, *ibid.* **106** 735, 1934.

254 Mackay, H. M. M. Anemia in Infancy. Prevalence and Prevention, *Arch. Dis. Childhood* **3** 117, 1928. Nutritional Anemia in Infancy. Some Observations on a Common Deficiency Disease, *Proc. Roy. Soc. Med. (Sect. Dis. Child.)* **22**, 29, 1929.

255 Parsons, L. G., and Hawksley, J. C. Studies in Anemias of Infancy and Early Childhood. Anhaematopoietic Anemias (Deficiency Diseases of the Erythron), Nutritional Anemia, and Anemias of Prematurity, Scurvy, and Coeliac Disease, *Arch. Dis. Childhood* **8** 117, 1933.

256 Mackay, H. M. M. Copper in the Treatment of Nutritional Anemia in Infancy, *Arch. Dis. Childhood* **8** 145, 1933.

Hawksley, Lightwood and Bailey<sup>257</sup> reported 12 cases of associated hypochromic anemia and achlorhydria occurring in infants and children after a test meal with alcohol. The anemia responded well to iron therapy, and they regarded it as probably identical with the simple achlorhydric anemia of adults.

#### ANEMIA ASSOCIATED WITH PUBERTY

Severe anemia of the hypochromic, microcytic type is occasionally encountered in young girls who have recently passed through adolescence. Such anemia is almost invariably the result of excessive or disordered menstruation dependent on endocrine dysfunction, and its discussion is not within the scope of this review. Chlorosis, formerly the outstanding member of this group of anemias, has so completely vanished from clinical experience that it is mentioned but to be dismissed.

#### HYPOCHROMIC ANEMIA IN ADULTS RELATED TO DIETARY DEFECTS AND DISORDERS OF DIGESTION

Unless associated with other factors such as loss of blood, pregnancy or impaired absorption from the digestive tract, a diet poor in iron rarely if ever leads to anemia in full grown persons. Lintzel,<sup>258</sup> after conducting experiments on iron balance, each of which lasted about two weeks, found that there was a balance in his subjects while they were receiving a daily intake varying between 0.9 and 63.8 mg. He concluded that the daily requirement for iron for an adult without complications is less than 0.9 mg. A diet furnishing so small a quantity of iron is difficult to devise, and is probably never encountered in practice. Davidson and his collaborators<sup>259</sup> found anemia (hemoglobin content less than 9.66 Gm per hundred cubic centimeters) in 45 per cent of 455 women, representatives of the poorer classes of Aberdeen. An analysis of many typical diets disclosed a uniformly low iron content, amounting in some instances to a daily supply of less than 6 mg. (A well planned diet supplies a daily intake of from 12 to 20 mg of iron.) However, gastric achlorhydria or marked hypochlorhydria was found in 89 per cent of these anemic women, and the remainder gave a history of gross loss of blood. Among male members of this social group anemia was not found except for obvious cause. The authors attributed the high

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257 Hawksley, J. C., Lightwood, R., and Bailey, U. M. Iron Deficiency Anemia in Children. Its Association with Gastro-Intestinal Disease, Achlorhydria, and Haemorrhage, *Arch. Dis. Child.* **9**: 359, 1934.

258 Lintzel, W. Zur Frage des Eisenstoffwechsels über den Eisenbedarf des Menschen, *Ztschr. f. Biol.* **89**: 342, 1929.

259 Davidson, L. S. P., Fullerton, H. W., Howie, J. W., Croll, J. M., Orr, J. B., and Godden, W. Observations on Nutrition in Relation to Anemia, *Brit. M. J.* **1**: 685, 1933.



incidence of anemia among women chiefly to an increased demand for iron dependent on frequent pregnancies or excessive loss of blood during menstruation and at parturition. They were able to effect a rapid cure by the administration of 6 Gm of ferric ammonium citrate daily. The problem of the bearing of nutrition on the formation of blood is by no means limited to a consideration of iron metabolism. Present knowledge of the dietary factors exerting direct and indirect influence on hematopoiesis as well as the larger question of the relationship between the blood level and the nutritional state of the entire organism has been excellently summarized by Davidson and Leitch <sup>260</sup>

During recent years increasing interest has been shown in an anemia of women which is not attributable to any single cause. The salient features of this condition are anemia of hypochromic, microcytic type occurring in women during the child-bearing period, persisting for long periods at a more or less constant level, usually associated with achlorhydria or hypochlorhydria and readily responsive to iron therapy, yet showing a strong tendency to recur on discontinuance of medication. To Faber <sup>261</sup> belongs the credit for the recognition of the importance of an anemia characterized by a low color index accompanying achylia gastrica. Kaznelson, Reimann and Weiner <sup>262</sup> provided the first complete description of this form of anemia. In addition to the characteristics listed previously, they mentioned the frequent occurrence of "pains in the bones," burning of the tongue with atrophy of the papillae, menstrual disorders, slight splenomegaly and koilonychia, a concavity of the nails giving them a spoon-shaped appearance. Examination of the sternal marrow of one of their patients revealed a great increase in the number of normoblasts, an observation later confirmed by Witts, <sup>263</sup> Dameshek <sup>264</sup> and Rosenthal and Abel <sup>265</sup>

Chronic dysphagia associated with anemia was described simultaneously by Kelly <sup>266</sup> and Paterson <sup>267</sup> in 1919. Three years later Vinson <sup>268</sup>

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260 Davidson, L. S. P., and Leitch, I. Nutritional Anemias of Man and Animals, *Nutrition Abstr. & Rev.* **3** 901, 1934

261 Faber, K. Achylia gastrica mit Anämie, *Med. Klin.* **5** 1310, 1909, *Anämische Zustände bei der chronischen Achylia gastrica*, *Berl. klin. Wchnschr.* **50** 958, 1913

262 Kaznelson, P., Reimann, F., and Weiner, W. Achylische Chloranämie, *Klin. Wchnschr.* **8** 1071, 1929

263 Witts, L. J. Achlorhydria and Anemia, *Practitioner* **124** 348, 1930

264 Dameshek, W. Primary Hypochromic Anemia (Erythro-Normoblastic Anemia). New type of Idiopathic Anemia, *Am. J. M. Sc.* **182** 520, 1931

265 Rosenthal, N., and Abel, H. A. Simple Achlorhydric Anemia, *Bull. New York Acad. Med.* **9** 24, 1933

266 Kelly, A. B. Spasm at the Entrance to the Oesophagus, *J. Laryng., Rhin. & Otol.* **34** 285, 1919

267 Paterson, D. R. A Clinical Type of Dysphagia, *J. Laryng., Rhin. & Otol.* **34** 289, 1919

268 Vinson, P. P. Hysterical Dysphagia, *Minnesota Med.* **5** 107, 1922

reported 69 cases and stated that Plummer had noted the condition in 1914. Moersch and Conner<sup>269</sup> in 1926 and Witts<sup>270</sup> in 1931 found achlorhydria in the majority of their cases, and this observation has been confirmed by most subsequent investigators, although Cameron<sup>271</sup> reported normal secretion of acid to be the rule in his case. The Plummer-Vinson syndrome, a term commonly applied to the association of functional dysphagia with hypochromic anemia, has been well reviewed by Suzman<sup>272</sup>. He and Wintrobe and Beebe<sup>273</sup> regard this syndrome in no sense as a distinct entity and consider dysphagia merely as an occasional complication of long-standing hypochromic anemia. With this view there is general accord.

A striking similarity may exist between the symptomatology of pernicious anemia and that of hypochromic anemia with achlorhydria. Such resemblance is probably based on the presence in both conditions of gastric anacidity, and its occurrence may be limited to those cases in which the secretory defect is of constitutional or hereditary origin. The gastric secretion of patients with anemia has been well studied by Davies<sup>274</sup> and by Hartfall with Witts<sup>275</sup>. The latter concluded that the important causes of achlorhydria are hereditary traits, gastritis and surgical procedures on the stomach. They described a family in which members of successive generations were found to have pernicious anemia, hypochromic anemia with achlorhydria or achlorhydria without anemia. Similar observations have been made by Gram,<sup>276</sup> Schulten,<sup>277</sup> Hurst<sup>278</sup> and Heath<sup>279</sup>. Hartfall and Witts<sup>280</sup> have demonstrated that

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269 Moersch, H. J., and Conner, H. M. Hysterical Dysphagia, *Arch Otolaryng* **4** 112 (Aug) 1926

270 Witts, L. J. Syndrome of Glossitis, Dysphagia and Anemia, *Guy's Hosp Rep* **81** 193, 1931

271 Cameron, M. Dysphagia and Anaemia, *J Laryng & Otol* **44** 168, 1929

272 Suzman, M. M. Syndrome of Anemia, Glossitis and Dysphagia. Report of Eight Cases, with Special Reference to Observations at Autopsy in One Instance, *Arch Int Med* **51** 1 (Jan) 1933

273 Wintrobe, M. M., and Beebe, R. T. Idiopathic Hypochromic Anemia, *Medicine* **12** 187, 1933

274 Davies, D. T. Studies on Achlorhydria and Anemia, *Quart J Med* **24** 447, 1931

275 Hartfall, S. J., and Witts, L. J. Gastric Secretion in Simple Achlorhydric and Allied Anemias, *Guy's Hosp Rep* **8** 3, 1933

276 Gram, H. C. A Study of the Development of Pernicious Anemia, *Folia haemat* **39** 461, 1930

277 Schulten, H. Zur Behandlung hypochromer Anamien mit maximalen Eisendosen, *Munchen med Wchnschr* **77** 355, 1930

278 Hurst, A. F. Achlorhydria and Achylia Gastrica, and Their Connection with Addison's Anaemia. Subacute Combined Degeneration Syndrome and Simple (Non-Addisonian) Achlorhydric Anaemia, *Quart J Med* **1** 157, 1932

the gastric secretion of persons with hypochromic anemia and achlorhydria is not deficient in the intrinsic factor of Castle, but that it may become so is evidenced by the reports of cases in which hypochromic anemia was ultimately replaced by pernicious anemia<sup>281</sup>

Limitations of space prohibit the discussion of a number of recent significant contributions to the subject of chronic hypochromic anemia<sup>282</sup> Much additional information will be found in the excellent articles of Witts<sup>283</sup> and Wintrobe and Beebe<sup>273</sup>

It is our opinion that the anemia under consideration cannot be regarded as a distinct disease Its general characteristics may be found

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279 Heath, C W Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia Study of Family in Which Both Conditions Occurred Singly and Combined, *Am J M Sc* **185** 365, 1933

280 Hartfall, S J, and Witts, L J Intrinsic Factor of Castle in Simple Achlorhydric Anemia, *Guy's Hosp Rep* **83** 24, 1933

281 (a) Witts, L J Varieties of Secondary Anemia and Their Treatment, *Lancet* **2** 531, 1931 (b) Minot, G R Idiopathic Hypochromic Anemia, *Libman Anniv Vols* **2** 831, 1932

282 (a) Reimann, F, and Fritsch, F Vergleichende Untersuchungen zur therapeutischen Wirksamkeit der Eisenverbindungen bei den sekundären Anämien, *Ztschr f klin Med* **115** 13, 1930 (b) Witts, L J Simple Achlorhydric Anaemia, *Guy's Hosp Rep* **80** 253, 1930 (c) Reimann, F, and Fritsch, F Experimentelle und klinische Untersuchungen über die Wirkung des Ferrum Reductum, *Ztschr f klin Med* **117** 304, 1931 (d) Mills, E S Idiopathic Hypochromemia, *Am J M Sc* **182** 554, 1931 (e) McCann, W S, and Dye, J Chlorotic Anemia with Achlorhydria, Splenomegaly and Small Corpuscular Diameter, *Ann Int Med* **4** 918, 1931 (f) Adamson, J D, and Smith, F H Chronic Chlorosis, *Canad M A J* **24** 793, 1931 (g) Davies, D T Simple Achlorhydric Anemia, *Lancet* **2** 385, 1931 (h) Waugh, T R Hypochromic Anemia with Achlorhydria, *Arch Int Med* **47** 71 (Jan) 1931 (i) Baur, M Die Pharmakologie des Eisens, *Ztschr f d ges phys Therap* **43** 89, 1932 (j) Beebe, R T, and Wintrobe, M M Effect on Idiopathic Hypochromic Anemia of Beef Steak (Hamburger Steak) Digested with Normal Gastric Juice, *Arch Int Med* **52** 464 (Sept) 1933 (k) Alt, H L "Hypoferric" Anemia, *Illinois M J* **64** 72, 1933 (l) Wright, C B Chronic Microcytic Anemia Its Relationship to Menstrual Disturbances and Achlorhydria, *Northwest Med* **32** 1, 1933 (m) Lundholm, I Achylia anami med nagelförändringar och glossit, *Svenska läk-tidning* **30** 244, 1933 (n) Mettier, S R, Kellogg, F, and Rinehart, J F Chronic Idiopathic Hypochromic Anemia Etiologic Relationship of Achlorhydria to Anemia, with Special Reference to the Effect of Large Doses of Iron, Organic (Dietary) Iron, and of Predigested Food upon Formation of Erythrocytes, *Am J M Sc* **186** 694, 1933 (o) Weber, F P, and Weisswange, W Simple Achlorhydric Anemia in Adult Males, *Brit M J* **2** 1066, 1933 (p) Burgher, G N, and Witts, L J Hypochromic Anemia in Men, *Guy's Hosp Rep* **84** 14, 1934 (q) Vaisey, A W Additional Symptomatology in Simple Achlorhydric Anemia, *Brit M J* **1** 143, 1934 (r) Meulengracht, E Simple Achylic Anemia After Gastro-Enterostomy and Partial Gastrectomy, *Acta med Scandinav* **81** 87, 1934 (s) Schur, M Ueber Eisenmangelanämien, *Wien Arch f inn Med* **25** 321, 1934 Footnotes 264 and 281b

283 Witts, L J Chronic Microcytic Anemia, *Brit M J* **2** 883, 1931

in any case of anemia due solely to chronic hemorrhage of long duration, whereas its specific features are limited to those cases exhibiting achlorhydria and are probably the result of complex secretory dysfunction of the stomach. Mettier and Minot<sup>284</sup> have claimed more effective utilization of iron for the production of hemoglobin from its administration in an acid than in an alkaline medium, and the studies of Reimann and Fritsch<sup>285</sup> yielded substantial evidence that the acidity of the gastric contents has a definite bearing on the absorption of iron. The majority of persons with achlorhydria do not have anemia, yet it is possible that in the presence of an acidity such extensive alterations may occur throughout the digestive tract that insufficient iron is absorbed to supply the needs for maintenance. It seems more probable, in view of the practical restriction of this type of anemia to the female sex, that other factors, such as repeated pregnancy or excessive menstruation, play contributory rôles. The work of Fowler and Barer<sup>286</sup> indicated that menorrhagia may be far more common than is generally supposed. Those authors found that the menstrual loss could be increased from five to twenty times the normal amount without recognition of any abnormality by the patient. Although the term "idiopathic hypochromic anemia" bestows an unwarranted individuality on the condition and implies that nothing is known of its etiology, it is probably less objectionable than other designations suggested for this type of anemia. "Simple achlorhydric anemia" and "achylic chloroanemia" are unsuitable, since gastric anacidity is not a prerequisite for this type of anemia. "Chronic chlorosis" is inappropriate as there is little clinical similarity between this condition and that designated as chlorosis.

The treatment of idiopathic hypochromic anemia involves the elimination, when possible, of those factors which may contribute to its causation. Such measures include correction of deficient diet, attention to sources of hemorrhage, avoidance of frequent pregnancy and attempts to improve the gastric secretion by the treatment of gastritis and the removal of septic foci.<sup>260</sup> Meulengracht<sup>213</sup> and Faber and Gram<sup>287</sup> were among the first to emphasize the value of large doses of preparations of iron in the treatment of this form of anemia. Their observations have been widely confirmed. Although simple ferrous compounds would seem to merit preference, in practice reduced iron and the com-

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284 Mettier, S. R., and Minot, G. R. Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, *Am J M Sc* **181** 25, 1931.

285 Footnotes 282 *a* and *c*.

286 Fowler, W. M., and Barer, A. P. Iron Retention Following Use of Ferric Ammonium Citrate in Hypochromic Anemia, *J A M A* **104** 144 (Jan 12) 1935.

287 Faber, K., and Gram, H. C. Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Arch Int Med* **34** 658 (Nov) 1924.

plex scale preparations, such as ferric ammonium citrate in adequate dosage are equally efficacious Mills,<sup>282d</sup> Adamson and Smith<sup>282f</sup> and Dameshek<sup>288</sup> have advised the administration of small quantities of copper (from 5 to 15 mg daily) as an adjunct to iron in the therapy of idiopathic hypochromic anemia Giffin and Watkins,<sup>289</sup> Heath,<sup>290</sup> Rosenthal and Abel<sup>265</sup> and we<sup>291</sup> have denied its value Other materials suggested for their possible beneficial effect on hematopoiesis in this type of anemia are a powdered extract of fetal calves' liver,<sup>292</sup> concentrated bile pigment<sup>293</sup> and a "pernicious anemia fraction" liver extract for parenteral administration<sup>294</sup>

## DEFINITE DISEASE ENTITIES OF THE BLOOD

### POLYCYTHEMIA

*Etiology*—Polycythemia associated with a marasmic bodily state develops in rats on a salt-poor ration with casein as the protein provided that a constant weight following a period of subnormal growth has been maintained for at least fifty-six days<sup>295</sup> Injections of cobalt chloride subcutaneously produce polycythemia in frogs, mice and guinea-pigs<sup>296</sup> An increase in the total cell volume has been produced by feeding cobalt to rats<sup>297</sup> It does not develop if the spleen is removed<sup>298</sup>

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288 Dameshek, W Primary Hypochromic Anemia Clinical Features, J A M A **100** 540 (Feb 25) 1933

289 Giffin, H Z, and Watkins, C H Treatment of Secondary Anemia, J A M A **95** 587 (Aug 23) 1930

290 Heath, C W Oral Administration of Iron in Hypochromic Anemia, Arch Int Med **51** 459 (March) 1933

291 Bethell, F H, Goldhamer, S M, Isaacs, R, and Sturgis, C C The Diagnosis and Treatment of the Iron-Deficiency Anemias, J A M A **103** 797 (Sept 15) 1934

292 Berglund, H, Watkins, C H, and Johnson, R Rapid Stimulation of Hemoglobin Synthesis in Secondary Anemias After Feeding Fetal Calf's Liver, Proc Soc Exper Biol & Med **25** 814, 1928

293 Patek, A J, Jr, and Minot, G R Bile Pigment and Hemoglobin Regeneration Effect of Bile Pigment in Cases of Chronic Hypochromic Anemia, Am J M Sc **188** 206, 1934

294 Murphy, W P Treatment of Secondary Anemia, with Special Reference to Use of Liver Extract Intramuscularly, Arch Int Med **51** 656 (May) 1933

295 Swanson, P P, and Smith, A H Inorganic Salts in Nutrition, Changes Induced in Blood by Ration Deficient in Inorganic Constituents, J Biol Chem **98** 479, 1932, Inorganic Salts in Nutrition Progressive Changes in Blood of Rats Maintained upon Ration Poor in Inorganic Salts *ibid* **98** 499, 1932

296 Sutter, Jean Cobalt et hyperglobulie, Compt rend Soc de biol **116** 994, 1934

297 Orten, J M, Underhill, F A, Mugrage, E R, and Lewis, R C Polycythemia in Rat on Milk-Iron-Copper Diet Supplemented by Cobalt, J Biol Chem **96** 11, 1932

298 Berwald, W P E, Arseneau, J H, and Dooley, M S Effect of Cobalt Sulphate on Erythrocyte Count of Splenectomized Albino Rat, Proc Soc Exper Biol & Med **32** 430, 1934

A familial, congenital type involving three brothers, a paternal uncle and two of his sons has been reported<sup>299</sup> The term "benign familial polycythemia" has been suggested to cover the nonsymptomatic polycythemia (with polyglobulia and splenomegaly) present in 7 members of a family<sup>300</sup>

Among the various theories as to the cause of polycythemia data in support of the following have been published recently It may be a clinical expression of chronic anoxemia with subsequent stimulation of the bone marrow as a result<sup>301</sup> The anoxemia may be a local factor in the bone marrow because of subintimal and adventitial fibrosis in the arteries and arterioles of the marrow<sup>302</sup> On testing the theory that polycythemia is due to an anoxemic stimulus, it was found that 2 patients living for two weeks in an oxygen tent (50 per cent oxygen) showed no significant change in the red blood cell count Cramplike pains, however, were relieved during the treatment<sup>303</sup> Data for the neoplastic nature of the disease have been presented<sup>304</sup> Others have considered that the secretion of too much of the intrinsic factor of Castle causes an increased production of red blood cells<sup>305</sup> Polycythemia may be present with achylia gastrica<sup>306</sup> Polyglobulia may be associated with certain tuberopituitary syndromes, with the production of a normal red blood cell count after removal of the pituitary tumor<sup>307</sup> An elevated erythrocyte count may accompany generalized tuberculosis with involve-

299 Mussio-Fournier, J C, and Lussich Siri, J J *Forme congenitale de la polycythémie idiopathique familiale*, Bull et mém Soc med d hôp de Paris **49** 121, 1933

300 Spodaro, A, and Forkner, C E *Benign Familial Polycythemia*, Arch Int Med **52** 593 (Oct) 1933 Wieland, E *Weitere Untersuchungen uber Polycythaemia Vera im Kindesalter*, Ztschr f Kinderh **53** 703, 1932

301 Waring, J J, and Yegge, W B *Polycythemia in Association with Pulmonary Disorders*, Ann Int Med **7** 190, 1933

302 Reznikoff, P, Foot, N C, Bethea, J M, and DuBois, E F *Racial and Geographic Origin of Patients Suffering from Polycythemia Vera and Pathological Findings in Blood Vessels of Bone Marrow*, Tr A Am Physicians **49** 273, 1934

303 Barach, A L, and McAlpin, K R *Negative Results of Oxygen Therapy in Polycythemia Vera*, Am J M Sc **185** 178, 1933

304 Weber, F P *Erythemia*, Proc Roy Soc Med **26** 362, 1933

305 Morris, R S, Schiff, L, and Foulger, M *Erythremia (Polycythemia Vera) Theory Regarding Etiology*, J Med **13** 318, 1932

306 Michaelides, F *Ueber einen Fall von Polycythaemia vera und Achylia gastrica*, Wien klin Wchnschr **45** 1250, 1932

307 Guillain, G, Lechelle, P, and Garcin, R *La polyglobulie, avec ou sans erythrose, de certains syndromes hypophysotuberiens (Retour a la normale du nombre des globules rouges apres exeresse chirurgicale d'une tumeur hypophysaire)*, Ann de med **31** 100, 1932 Moehlig, R C, and Bates, G S *Influence of Pituitary Gland on Erythrocyte Formation*, Arch Int Med **51** 207 (Feb) 1933 Baserga, A *Poliglobulie da lesioni diencefalo-ipofisarie*, Policlinico (sez med) **41** 17, 1934

ment of the spleen<sup>308</sup> Polycythemia caused by epinephrine is inhibited by the injection of yohimbin<sup>309</sup> Venesection and roentgen irradiation over the long bones do not cause an increase in the production of reticulocytes such as follows treatment with phenylhydrazine<sup>310</sup>

*Treatment*—Treatment with phenylhydrazine hydrochloride may be continued for long periods, and some patients have been able to discontinue the drug entirely after from two to four years of treatment<sup>311</sup> Acetylphenylhydrazine has some advantages over phenylhydrazine hydrochloride (decreased toxicity, more easily regulated dosage and greater margin of safety)<sup>312</sup> Roentgen irradiation in comparatively small doses over many parts of the body besides the long bones at two to four day intervals produced a remission in 1 patient<sup>313</sup> Others have produced remissions by intensive treatments over the long bones<sup>314</sup> In a patient who did not respond to roentgen therapy, small doses of phenylhydrazine (0.01 Gm) twice weekly gave a satisfactory remission without toxic symptoms<sup>315</sup> The erythrocyte count may be reduced with the administration of n-propyl disulphide<sup>316</sup> Raw onion has also been used<sup>317</sup>

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308 Heymann, K. G., and Bussel, R. Ueber Polyglobulie bei generalisierter Tuberculose und ihre Beziehung zur Milz, *Jahrb f Kinderh* **136** 26, 1932  
Margolis, A., and Warszawski, S. Case of Tuberculous Splenomegaly with Polycythemia, *Polska gaz lek* **12** 645, 1933

309 Simoes-Raposo, L., Fevereiro, A., and Leite, S. Mecanisme de l'erythrocytose Polyglobulie adrenalinique et hypoglobulie yohimbique, *Compt rend Soc de biol* **109** 1044, 1932

310 Falconer, E. H. Treatment of Polycythemia Reticulocyte Response to Venesection, Phenylhydrazin and Radiation, *Ann Int Med* **7** 172, 1933

311 Giffin, H. Z., and Allen, E. V. The Control and Complete Remission of Polycythemia Vera Following the Prolonged Administration of Phenylhydrazin Hydrochlorid, *Am J M Sc* **185** 1, 1933  
Stealy, C. L. Polycythemia Vera Report of Case Treated with Phenylhydrazine Hydrochloride Over a Period of Seven and One Half Years, *J A M A* **98** 1714 (May 14) 1932  
McAlpin, K. R., and Edsall, K. S. Polycythemia Vera Report of Ten Cases Treated with Phenylhydrazine, *New York State J Med* **33** 1039, 1933

312 Stone, C. T., Harris, T. H., and Bodansky, M. Treatment of Polycythemia Vera Report of Two Cases, *J A M A* **101** 495 (Aug 12) 1933

313 Chambers, W. E. Polycythemia Vera, *M Bull Vet Admin* **9** 428, 1933

314 de Meyer, J., and Sluys, F. Deux cas de maladie de Vaquez (polycythemia rubra vera) traites par la roentgentherapie de la moelle osseuse, *Scalpel* **85** 259, 1932  
Rossoni, R. Contributo al trattamento radioterapico del m di Vaquez, *Radiol med* **19** 156, 1932  
Sgalitzer, M. Rontgenallgemeinbestrahlung bei Polyglobulie, *Fortschr a d geb d Rontgenstrahlen* **46** 90, 1932

315 Hare, D. C. Splenomegalic Polycythemia Treated with Minimal Doses of Phenylhydrazine, *Proc Roy Soc Med* **26** 363, 1933

316 Sharp, E. A., Vonderherde, E. C., and McKean, R. M. Beneficial Effect of N-Propyl Disulphide in Polycythemia Vera Case Report, *J Michigan M Soc* **31** 394, 1932

317 Boissannas, L. Un cas de maladie de Vaquez traite avec succes par l'oignon cru, *Rev franç de pediatrie* **8** 745, 1932

After the administration of phenylhydrazine there is a temporary negative nitrogen balance (increased excretion of urea, proteinuria, decreased intake of nitrogen) The total consumption of oxygen is parallel to the endogenous nitrogen catabolism The liberated iron is retained by the body<sup>318</sup> Urea and bilirubin are formed more rapidly than they are excreted The phosphorus balance is approximately maintained Leukocytosis and reticulocytosis are features There is a decrease in the viscosity of the blood<sup>318a</sup>

*Symptoms*—Ménière's vertigo may accompany the polycythemia<sup>319</sup> Necrosis of the extremities may be a complication<sup>320</sup>

*Prognosis*—The disease may terminate in anemia<sup>321</sup> A remission of eleven years, with subsequent relapse, has been noted<sup>322</sup>

#### PURPURA HAEMORRHAGICA

Purpura may result from many causes, and various forms have been classified under different headings A review of the literature shows multiple classifications, all of them are complex,<sup>323</sup> and their clinical value is somewhat doubtful The three factors which determine the bleeding are (a) the platelets, (b) the permeability of the capillaries and (c) the blood plasma It is thought that the diminution in the number of platelets is due either to their deficient formation in the bone marrow or to their increased destruction by the reticulo-endothelial system (primarily the spleen) Some authors are of the opinion that the decreased number of platelets is the result of hemorrhage rather than the cause, the thrombocytes being withdrawn from the circulation and fixed in the bleeding areas as a defense mechanism<sup>324</sup>

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318 (a) Barer, A., Paul, W. D., and Baldrige, C. W. Studies in Relationships Between Oxygen Consumption and Nitrogen Metabolism. III. In Polycythemia Vera, *J. Clin. Investigation* **13** 15, 1934 (b) Reznikoff, P. Iron Metabolism Studies, *ibid* **11** 807, 1932

319 Bieling, K. Menierescher Schwindel bei Polyzythämie, *Med. Klin.* **29** 1410, 1933 Koch, J., and Rothmann, H. Meniereartige Erscheinungen bei Polyzythämie, *ibid* **29** 320, 1933

320 Kheneberger, C. Erfrierungseinwirkung als Unfall im Sinne von Verschlimmerung, anerkannt bei Gefassverschlüssen der Erythraemia vera, *Monatsschr. f. Unfallh.* **40** 276, 1933 Becker, F. Extremitätennekrose bei Polycythemia Vera, *Klin. Wchnschr.* **11** 1260, 1932

321 Platt, R. Case of Polycythemia Rubra Developing Anaemia, *Brit. M. J.* **1** 750, 1932

322 Falconer, E. H. An Unusual Remission in Polycythemia Vera, *J. A. M. A.* **101** 1633 (Nov. 18) 1933

323 Wyllie, W. G., and Ellis, R. W. B. Clinical Interpretation of Some Haemorrhagic States, *Arch. Dis. Childhood* **6** 313, 1931

324 Rolleston, Humphrey. The History of Hematology, *Proc. Roy. Soc. Med.* **27** 1161, 1934



Thrombocytopenic purpura may be hereditary or acquired. Often the etiology is not known. It is usually associated with diseases of the bone marrow and spleen or is the result of infection or drugs. Alterations in the permeability of the vascular membranes associated with purpura may be the result of food deficiency, allergy, infection and toxins.<sup>325</sup> It is absolutely necessary to determine the cause of purpura before instituting treatment, and as this cannot always be done many failures of therapy result.

Although splenectomy has often been associated with remarkable improvement, it likewise has proved of no benefit.<sup>326</sup> If the platelets are being destroyed in excessive numbers by the spleen, its surgical removal is indicated, however, it is of little value to perform a splenectomy if the decreased number of platelets is the result of a failure of formation in the bone marrow. It must also be remembered that the operation itself is associated with a high mortality rate. Because of the latter fact, ligation of the splenic artery has been recommended as a substitute for splenectomy.<sup>326a</sup> Foci of infection should always be removed,<sup>327</sup> as well as the source of any toxic substances. Hemorrhagic infectious diseases are often improved by the administration of calcium salts or gelatin intravenously.<sup>326f</sup>

Purpura associated with food deficiency may be alleviated by a well balanced diet especially rich in vitamins and having a high protein and fat content.<sup>326f</sup> Thromboplastic agents have been recommended to aid clotting, and although their efficacy has been proved in vitro there are little if any clinical data to support the laboratory observations.<sup>328</sup> A similar situation exists with radium.<sup>329</sup> Both cures and

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325 Kugelmass, I. N. Management of Hemorrhagic Problems in Infancy and Childhood, *Tr. Sect. Pediat., A. M. A.*, 1932, p. 147, *New York State J. Med.* **33** 434, 1933.

326 (a) Pemberton, J. deJ. The Diagnosis and Treatment of Purpura Hemorrhagica, *Am. J. Surg.* **24** 793, 1934. (b) Vastola, A. P. Acute Thrombocytopenic Purpura Hemorrhagica and Its Treatment, *M. J. & Rec.* **133** 603, 1931. (c) Fagge, H. Essential Thrombocytopenia with Delayed Response to Splenectomy, *Guy's Hosp. Rep.* **84** 72, 1934. (d) Kracke, R. R. Effect of Splenectomy in Purpuric Diseases, *South. Surgeon* **2** 203, 1933. (e) Eliason, E. L., and Ferguson, L. K. Splenectomy in Purpura Hemorrhagica, *Ann. Surg.* **96** 801, 1932. (f) Kugelmass, I. N. Management of Hemorrhagic Problems in Infancy and Childhood, *J. A. M. A.* **99** 895 (Sept. 10) 1932. (g) Jones, H. W., and Tocantins, L. The Treatment of Purpura Hemorrhagica, *ibid.* **100** 83 (Jan. 14) 1933.

327 Footnotes 326a and g.

328 Hoffmann, S. S. Treatment of Henoch's Purpura with Haemoplastin, *J. M. A. South Africa* **5** 600, 1931. Gold, H. Control of Hemorrhage by Thromboplastic Agents, *Internat. Clin.* **2** 293, 1932.

329 Hoffman, J. M. Radium in Treatment of Diseases with Subcutaneous or Mucous Membrane Hemorrhages, Preliminary Report, *Radiology* **14** 136, 1930.

failures have been reported with the administration of liver<sup>330</sup> Snake venom<sup>331</sup> has become the most recent fad, but there are insufficient data at present to estimate its true clinical worth. A conservative attitude must be adopted concerning the value of the various therapeutic agents recommended, as it must be kept in mind that a spontaneous cure is not uncommon.

#### HEMOPHILIA

Although the Talmud has a reference to hemophilia, the first clear description of the disease was made in 1803 by Otto. This disease occurs in males and is transmitted by females. Persons with hemophilia usually have more daughters than sons, whereas transmitters have more sons than daughters. Approximately 71 per cent of transmitters' sons have hemophilia, less than 10 per cent of transmitters' daughters have normal sons and from 3 to 7 per cent of daughters of a hemophiliac parent have normal sons.<sup>332</sup>

The diagnosis of hemophilia is based on the following findings: heredity, its occurrence in males, a history of repeated hemorrhages, prolonged clotting time and a normal bleeding time.<sup>333</sup> A study of the elements of the blood reveals a low prothrombin and a high antithrombin content with a slow rate of disintegration of the platelets.<sup>334</sup> Some authors have expressed the belief that the disease is due to faulty development of the liver while others are of the opinion that it is caused by an endocrine deficiency.<sup>335</sup>

Although various types of therapy have been employed, there is no specific treatment for the malady. Some of the more common agents are whole blood, citrated blood, human plasma, human serum, defibrinated blood, horse serum, hemostatic preparations, fibrinogen and cephalin in suspension, calcium chloride, sodium citrate, protein shock, liver and its derivatives, whole ovary and ovarian extracts and a special dietary regimen. The therapy may be divided into two stages: prophylactic and treatment of the immediate hemorrhage.

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330 Jacob, F. H., and Clapperton, T. Cure of Thrombopenic Purpura by Liver, *Brit M J* **1** 823, 1930. Witts, L. J. Inefficacy of Liver Treatment in Essential Thrombopenia, *Lancet* **1** 809, 1931.

331 Stockton, M. R., and Franklin, G. C. H. Antivenin Therapeutics in Purpura. Case Report, *J A M A* **96** 677 (Feb 28) 1931. Taylor, K. P. A. Antivenin in Thrombocytopenic Hemorrhage. Importance of Bothropic Type, *Am J Surg* **21** 285, 1933.

332 Birch, C. L. Hemophilia, *J A M A* **99** 1566 (Nov 5) 1932.

333 Kugelmass, I. N. Diagnosis and Management of Hemophilia in Childhood, *New York State J Med* **32** 660, 1932.

334 Kugelmass, I. N. Mechanism of Hemophilia in Infancy and in Childhood, *Am J Dis Child* **44** 50 (July) 1932.

335 Mills, C. A. Hemophilia, *J Lab & Clin Med* **17** 932, 1932.

As a result of recent experimental work<sup>336</sup> it has been stated that the urine of persons with hemophilia does not contain the female sex hormone, however, all authors do not agree with this<sup>337</sup> Based on this theory of endocrine deficiency, whole ovary and ovarian extracts have been administered to prevent episodes of bleeding The results have been variable<sup>338</sup> Tissue extracts<sup>339</sup> and ultraviolet rays<sup>340</sup> likewise have been of little value Some authors are of the opinion that a diet high in vitamins and protein increases the coagulation time<sup>341</sup> Saliva has aided coagulation of blood in vitro,<sup>342</sup> but its clinical value has not been demonstrated Sensitization with animal serum<sup>343</sup> still remains the most satisfactory form of prophylactic therapy

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336 Birch, C L Hemophilia and Female Sex Hormone (in Urine) Preliminary Report, *J A M A* **97** 244 (July 25) 1931 Footnote 334

337 Brown, R L, and Albright, F Estrin Therapy in Case of Hemophilia, *New England J Med* **209** 630, 1933 Chew, W V, Stetson, R P, Smith, G Van S, and Smith, O W Estrogenic, Luteal and Gonadotropic Hormones in Hemophilia, *Arch Int Med* **55** 431 (March) 1935

338 Birch, C L Hemophilia (Platelet Study and Treatment with Ovarian Extract and Transplantation), *Proc Soc Exper Biol & Med* **28** 752, 1931 Foord, A G, and Dysart, B R Treatment of Hemophilia by Ovarian Extract by Birch's Method, *J A M A* **98** 1444 (April 23) 1932 Kimm, H T, and Van Allen, C M Hemophilia Prevention and Treatment of Bleeding with Ovarian Extract, *ibid* **99** 991 (Sept 17) 1932 Freeman, E T Notes on Hemophilia with Recent Experiments on Clotting Time and Their Influence on Treatment (Ovarian), *Irish J M Sc* 1933, p 122 Stetson, R P, Forkner, C E, Chew, W B, and Rich, M L The Negative Effect of Prolonged Administration of Ovarian Substance in Hemophilia, *J A M A* **102** 1122 (April 7) 1934 Blalock, A Amputation of Arm of Patient with Hemophilia, *ibid* **99** 1777 (Nov 19) 1932 Brem, J, and Leopold, J S Ovarian Therapy Relationship of the Female Sex Hormone to Hemophilia, *ibid* **102** 200 (Jan 20) 1934 Spoto, J S Treatment of Hemophilia with Ovarian Extract, Report of Two Cases, *J Florida M A* **20** 9, 1933 Hirst, J C The Influence of Female Sex Hormones upon Blood Coagulation of the Newborn, *Am J Obst & Gynec* **26** 217, 1933 White, C E Treatment of Hemophilia with Theelin, *J Oklahoma M A* **25** 304, 1932 Footnotes 332 and 336

339 Burns, E L, Scharles, F H, and Aitken, L F Effect of Mixtures of Tissue Extracts and Blood Sera of Various Animals on Coagulation of Blood, *Am J Physiol* **97** 233, 1931

340 Sanford, H N, Gasteyer, T H, and Wyatt, L Substances Involved in Coagulation of Blood of New-Born Effect of Ultraviolet Radiation and Viosterol (Irradiated Ergosterol), *Am J Dis Child* **43** 566 (March) 1932 Phillips, R A, Robertson, D F, Corson, W C, and Irwin, G F Effect of Irradiated Ergosterol on Thrombocytes and Coagulation, *Ann Int Med* **4** 1134, 1931

341 Kugelmass, I N, and Samuel, E L Avitaminosis and Blood Clotting Function, *Am J Dis Child* **43** 52 (Jan) 1932, Dietary Protein and Blood Clotting Function, *ibid* **41** 48 (Jan) 1931

342 Bellis, C J, Birnbaum, W, and Scott, F H Coagulation—Effect of Saliva, *Proc Soc Exper Biol & Med* **29** 1107, 1932

343 Eley, R C, and Clifford, S H Hemophilia Treatment by Protein Sensitization, *Am J Dis Child* **42** 1331 (Dec) 1931 Footnote 333

Acute hemorrhages are best treated by compression, repeated injection of whole blood into the buttocks, multiple transfusions and administration of epinephrine<sup>344</sup>

#### LYMPHOGRANULOMA HODGKIN'S DISEASE

Numerous reports of cases emphasize the occurrence of lesions in the bones, stomach, spleen, liver, spinal cord (with compression symptoms), mediastinum (with mediastinal pleurisy), skin, tonsils, sternum, thyroid and subdural space. Cases in which tuberculosis, ileus and the symptoms of gastric ulcer were associated with the disease are recorded.

From a study of 108 collected cases of Hodgkin's disease in children, Smith<sup>345</sup> concluded

1 Hodgkin's disease shows an even greater tendency to attack the male sex in childhood than in other age periods. Over four fifths (81.5 per cent) of 108 collected childhood cases were in boys. In the author's 23 cases, 91.1 per cent were in boys. There is also a marked predominance of the male sex in childhood cases of leukemia and lymphosarcoma.

2 The onset of Hodgkin's disease in childhood showed no significant relationship to preceding illness or to foci of infection, in 23 cases studied. A familial predisposition to the disease is sometimes seen.

3 Secondary invasion with tuberculosis is fairly frequently observed in children with Hodgkin's disease, and the two diseases may coexist for years in the same patient. There is a marked tendency for the tuberculin test to remain negative in the presence of Hodgkin's disease, both in children and in adults. The disease may cause tuberculin anergy.

4 In none of 5 children with Hodgkin's disease tested with avian tuberculin was there a positive reaction.

5 Results of tuberculin tests are not satisfactory evidence as to an etiologic relationship between the two diseases.

6 The histopathology as well as the sex ratios of Hodgkin's disease in childhood are suggestive of a neoplastic rather than a granulomatous process.

7 In childhood the left cervical region is considerably more frequently invaded early than the right, which may be evidence that the disease often has an unsuspected abdominal onset. Invasion of mediastinal glands is common, and often not apparent without x-ray examination. Splenic and hepatic involvement is common late in the disease and is of bad prognostic import. Cutaneous manifestations are comparatively infrequent in childhood.

8 Septic and recurrent relapsing (Pel-Ebstein) temperatures are not rare in children with Hodgkin's disease, and are bad prognostic signs.

9 Blood studies of 20 children with Hodgkin's disease showed a progressive anemia, and a tendency to leucopenia and to an increase in monocytes.

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344 Pereira, H., and Pereira, A. Treatment of Haemophilic Diseases by Whole Blood, *Brit. M. J.* **1** 283, 1930. Kugelmass, I. N. Clinical Control of Chronic Hemorrhagic States in Childhood, *J. A. M. A.* **102** 287 (Jan. 27) 1934. Footnote 335.

345 Smith, C. A. Hodgkin's Disease in Childhood. Clinical Study with Résumé of Literature to Date, *J. Pediat.* **4** 12, 1934.

10 Though fulminating, rapidly fatal Hodgkin's disease is common in childhood, the average duration of 16 fatal cases was 3.45 years. Five living patients have survived an average of 4.2 years. The average duration of 41 fatal cases from the literature was 1.8 year. Cases beginning in childhood and now alive twelve and fifteen years after onset have been seen in this clinic.

11 The use of roentgen irradiation is recommended, though absolute proof of its ultimate benefit cannot be adduced from our cases. A program for its use is suggested.

As to duration and prognosis Craver<sup>346</sup> found

Of 310 cases of Hodgkin's disease, 125 proved by biopsy, 10.3 per cent showed a survival following irradiation of 5 years or over—of the proven cases, 12 per cent. Five year survivors averaged 10 years younger (34 years of age) than a group that had survived 6 months or less, though extremes of age were the same in the two groups. The difference in survival of the two groups is apparently due to difference in virulence of the disease. This, however, showed no correlation with the histologic appearance of nodes removed at biopsy. Favorable features were localization in one area, combined with early thorough treatment, absence of leukocytosis or leukopenia, gain in weight after irradiation. Fever, marked pruritis and splenomegaly were apparently unfavorable signs.

Leucutia,<sup>347</sup> in an analysis of 2,425 collected cases, found that 30 per cent of the patients with lymphosarcoma survived for five years and from 10 to 15 per cent for ten years. In the remaining groups, the expectation of life has been increased by adequate treatment from two and one-half to three and one-twelfth years.

In Hodgkin's disease, the 5 year survival reaches 15 per cent to 33 per cent, but the cases in the great majority remain carriers of the disease, necessitating frequent resumption of irradiation. A ten year survival or cure occurs in 8 per cent of the cases or less. In those who died within the first 5 years, the average expectancy of life was increased from 2 to 3½ years. The symptomatic improvement is nearly always marked but not so spectacular as in lymphosarcoma.

Different workers recommend varying dosages of roentgen ray. McAlpin and Golden<sup>348</sup> recommended small doses at frequent intervals, and Levitt<sup>349</sup> mentioned doses "considerably below the tolerance of the skin and healthy tissues," and considered that the so-called roentgen ray bath (generalized exposures of the trunk and abdomen to repeated small doses) has great possibilities.

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346 Craver, Lloyd F. Five-Year Survival in Hodgkin's Disease, *Am J M Sc* **188** 609, 1934.

347 Leucutia, T. Irradiation in Lymphosarcoma, Hodgkin's Disease and Leukemia (a Statistical Analysis), *Am J M Sc* **188** 612, 1934.

348 McAlpin, K. R., and Golden, Ross. Roentgen Treatment of Lymphoblastoma (Hodgkin's Disease), *Am J Roentgenol* **29** 83, 1933.

349 Gordon, M. H., Gow, A. E., Levitt, W. M., and Weber, F. P. Recent Advances in the Pathology and Treatment of Lymphadenoma, *Proc Roy Soc Med* **27** 1035, 1934.

Of 172 patients with Hodgkin's disease, 27 were found to have involvement of the bones. The vertebrae and pelvis are most frequently affected. Osteoplastic and osteolytic changes with collapse of the vertebrae occur. For treatment, Heublein's method of prolonged continuous low intensity irradiation of the entire body has been recommended. For the gross lesions of the bones, single large erythema doses or fractional doses of high voltage roentgen rays are used by some. After treatment relief from pain and healing processes in the bones have been noted.<sup>350</sup>

Gordon's test<sup>351</sup> for Hodgkin's disease consists in the inoculation of the material from lymph nodes into the brains of rabbits. With material from a patient with true Hodgkin's disease a paralysis of the hindlegs with ataxia is produced, whereas the results are negative when normal lymphatic tissue is used, or lymphosarcoma, leukemia or tuberculous tissue, bacteria, sterile milk peptone, and albuminoid substance and lecithin sodium nucleinate, quinine, ethyl carbamate (urethane) or powdered glass. Of 5 patients with Hodgkin's disease 3 gave a positive reaction, 1 a doubtful reaction and 1 a negative reaction.<sup>351a</sup>

Avian tubercle bacilli were found in 6 of 8 cases of Hodgkin's disease. It was not possible to infect rabbits, guinea-pigs, pigeons or chickens by intravenous, intraperitoneal or intramuscular injection.<sup>352</sup> Steiner<sup>353</sup> was unable to detect avian tubercle bacilli in tissue from 15 patients with Hodgkin's disease, and he was not able to transmit the disease to animals by the injection of glandular material. Gordon<sup>349</sup> had similar results.

On the basis that Hodgkin's disease may be caused by avian tuberculosis, chicken serum has been given experimentally with conclusive results.<sup>354</sup> Specific vaccines have so far been ineffective.<sup>349</sup> Infection has been suggested as a predisposing factor to lymphoblastoma.<sup>355</sup> Krumbhaar<sup>356</sup> favors the theory of infection rather than one of neoplastic origin of Hodgkin's disease, but Weber<sup>349</sup> considers it as having a "neoplastic trend."

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350 Craver, L. F., and Copeland, M. M. Changes in the Bone in Hodgkin's Granuloma, *Arch Surg* **28** 1062 (June) 1934.

351 (a) Van Rooyen, C. E. A Biological Test in the Diagnosis of Hodgkin's Disease, *Brit M J* **1** 644, 1933. (b) Footnote 349.

352 Van Rooyen, C. E. Aetiology of Hodgkin's Disease with Special Reference to B. Tuberculosis Avis, *Brit M J* **1** 50, 1933.

353 Steiner, P. E. Hodgkin's Disease. Search for Infective Agent and Attempts at Experimental Reproduction, *Arch Path* **17** 749 (June) 1934.

354 Barrett, N. R., and Bond, L. T. Serum Treatment of Hodgkin's Disease with Account of Four Cases Treated, *Lancet* **2** 855, 1933. Pulvertaft, R. J. V. Treatment of Lymphadenoma with Chicken Serum, *ibid* **2** 857, 1933.

355 Desjardins, A. U. The Etiology of Lymphoblastoma, *J A M A* **103** 1033 (Oct 6) 1934.

356 Krumbhaar, E. B. Is Typical Hodgkin's Disease Infection or Neoplasm? *Am J M Sc* **188** 597, 1934.

## LEUKEMIA

*Types and Incidence*—During the past few years increased prominence has been given to monocytic leukemia, at least 56 cases having been reported during a three year period<sup>357</sup> It is possible that many cases of this type were formerly considered as instances of atypical myelogenous leukemia Many of the cases reported as being "monocytic" were of other types, so that it is not possible to estimate the relative incidence of the disease with any degree of accuracy In most of the cases reported the course has been fairly acute, and the condition has not been influenced favorably by roentgen therapy

Among other unusual types of leukemia reported are eosinophilic,<sup>358</sup> megakaryoblastic<sup>359</sup> and plasma cell leukemia<sup>360</sup> Cases of leukemia have been reported from Italy, Russia, Germany, England, Poland, Spain, France, the United States, Japan, The Netherlands, Chile and other countries, suggesting a world-wide incidence Leukemia-like conditions have been reported in dogs, mice and fowl A case of myelogenous leukemia has been reported in a 5 week old infant<sup>361</sup> The occurrence of leukemia in two brothers has been noted<sup>362</sup>

*Etiology*—A leukemia-like picture has been produced in mice by the weekly injection of benzene in olive oil,<sup>363</sup> and cases in human beings

357 Doan, C A, and Wiseman, B K The Monocyte, Monocytosis, and Monocytic Leukosis Clinical and Pathological Study, *Ann Int Med* **8** 383, 1934  
Clough, P W Monocytic Leukemia, *Bull Johns Hopkins Hosp* **51** 148, 1932  
Forkner, C E Clinical and Pathologic Differentiation of Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, *Arch Int Med* **53** 1 (Jan) 1934  
Farrar, G E, and Cameron, J D Monocytic Leukemia with Data on the Individuality and Development of the Monocyte, *Am J M Sc* **184** 763, 1932  
Levine, V Monocytic Leukemia Report of Nine Cases, *Folia haemat* **52** 305, 1934

358 McCowen, G R, Parker, H B, and Panton, P N Case of Acute Eosinophilic Leukemia, *J Roy Nav M Serv* **18** 131, 1932

359 von Boros, J, and Korenyi, A Ueber einen Fall von akuter Megakaryoblastenleukemie, zugleich einige Bemerkungen zum Problem der akuten Leukemie, *Ztschr f klin Med* **118** 697, 1931

360 Muller, G L, and McNaughton, E Multiple Myeloma (Plasmacytoma) with Blood Picture of Plasma Cell Leukemia Report of Two Cases, *Folia haemat* **46** 17, 1931

361 Giblin, J Case of Myelogenous Leukemia Occurring in Infant Five Weeks Old, *Arch Pediat* **50** 662, 1933

362 Petri, Sven Ueber familiares Auftreten der Leukemie, *Acta path et microbiol Scandinav* **10** 330, 1933

363 Lignac, G O E Benzol-leukemie bei Menschen und weissen Mause, *Klin Wchnschr* **12** 109, 1933, comment by Teleky, *ibid* **12** 472, 1933

have been reported.<sup>364</sup> Malaria was described as a predisposing factor in 1 case<sup>365</sup> and nonfilarial elephantiasis in another.<sup>366</sup>

Lymphatic leukemia may be transmitted in certain strains of mice by inoculation of material derived from mice with spontaneous leukemia.<sup>367</sup> Efforts to separate the active agent from the cells in the material used for inoculation have not been successful, as in the case of the leukemia-like condition in chickens.<sup>368</sup>

*Pathology*—Abnormalities in the mitotic division of leukocytes of myelogenous leukemia, nonspecific but resembling the condition in cancer, have been noted in tissue cultures.<sup>369</sup> The dividing leukoblasts may show only half the somatic number of chromosomes,<sup>370</sup> and the "mitosis angle" may differ from normal.<sup>371</sup> The elevated basal metabolic rate may be associated with the disturbance in thyroid function from leukemic invasion.<sup>372</sup> Metastatic calcification of the endocardium, pulmonary veins, aorta and main pulmonary artery, lungs and kidneys has been noted, with calcium mobilized from the long bones.<sup>373</sup> Localized tumors (myeloblastic sarcoma) have been observed during the course of the

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364 Falconer, E. H. Instance of Lymphatic Leukemia Following Benzol Poisoning, *Am J M Sc* **186** 353, 1933. Weil, P. E. La leucémie post-benzolique, *Bull méd, Paris* **46** 750, 1932.

365 Reynolds, F. H. Case of Lymphatic Leukaemia, *Indian M Gaz* **68** 84, 1933.

366 Larrabee, R. C., and Peers, J. H. A Case of Nonfilarial Elephantiasis Terminating with Aleukemoid Anemia, *J A M A* **102** 1936 (June 9) 1934.

367 Richter, M. N., and MacDowell, E. C. Studies on Mouse Leukemia, Relation of Cell Death to Potency of Inoculated Cell Suspensions, *J Exper Med* **57** 1, 1933.

368 Feldman, W. H., and Olson, C. The Pathology of Spontaneous Leukosis of Chickens, *J Am Vet M A* **82** 875, 1933. Furth, J. Lymphomatosis, Myelomatosis and Endothelioma of Chickens Caused by Filterable Agent, Transmission Experiments, *J Exper Med* **58** 253, 1933. Studies on Nature of Agent Transmitting Leucosis of Fowls, Resistance to Desiccation, to Glycerin, to Freezing and Thawing, Survival at Ice Box and Incubator Temperatures, *ibid* **55** 495, 1932. Studies on Nature of Agent Transmitting Leucosis in Fowls Its Concentration in Blood Cells and Plasma and Relation to Incubation Period, *ibid* **55** 465, 1932. Immunity Phenomena in Transmissible Leucosis of Fowl, *Proc Soc Exper Biol & Med* **29** 1236, 1932.

369 Andres, A. H., and Shiwago, P. I. Karyologische Studien und myelöischer Leukämie des Menschen, *Folia haemat* **49** 1, 1933.

370 Groat, W. A. Leukemias Showing Haploid Leukoblasts Undergoing Mitotic Division in Circulating Blood, *Am J M Sc* **185** 624, 1933.

371 Hittmair, A. Ueber Mitosenwinkelmessung, *Folia haemat* **47** 230, 1932.

372 Friedgood, H. B. Relation of Sympathetic Nervous System and Generalized Lymphoid Hyperplasia to Pathogenesis of Exophthalmic Goiter and Chronic Lymphatic Leukemia, *Am J M Sc* **183** 841, 1932.

373 De Santo, D. A. Metastatic Calcification Occurring in Myelogenous Leukemia, *Am J Path* **9** 105, 1933.



disease<sup>374</sup> From studies of sections of bone marrow Jaffé<sup>375</sup> concluded that the anemia which occurs in chronic myelogenous leukemia is due not to the replacement of the erythropoietic tissues but to excessive destruction of red cells (hemosiderosis) The same author noted the presence of active tuberculosis in 3 of 30 cases of chronic myelogenous leukemia In none of these was there any evidence that the leukemic cells (myeloblasts) took part in the defense against the infection<sup>376</sup> Lymphosarcoma may terminate with a leukemic blood picture<sup>377</sup> Leukemic infiltration of the bones with periosteal thickening, cortical erosion and medullary rarefaction has been noted<sup>378</sup> Aleukemic myelosis may be associated with osteosclerosis and fibrosis of the bone marrow and splenomegaly<sup>379</sup>

*Symptomatology*—A variation in symptoms has been the feature in reports of cases no enlargement of the spleen or lymph nodes,<sup>380</sup> cutaneous infiltrates<sup>381</sup> with changes in the nasal mucosa, coexistence with tuberculous adenitis, miliary tuberculosis, isolated symmetrical

374 Dubois, F S Myeloblastic Sarcoma of Scapula Associated with Chronic Splenomyelogenous Leukemia, *Am J Path* **9** 113, 1933

375 Jaffé, R H Morphology of Inflammatory Defense Reactions in Leukemia, *Arch Path* **14** 177 (Aug) 1932, Erythropoiesis in Leukemia, *Folia haemat* **49** 51, 1933

376 Jaffe, R H Tuberculosis and Leukemia, *Am Rev Tuberc* **27** 32, 1933

377 Kato, K, and Brunschwig, A Acute Leukemia Following Lymphosarcoma, *Arch Int Med* **51** 77 (Jan) 1933

378 Smith, C H Leukopenic Myeloid Leukemia Associated with Arthritis, *Am J Dis Child* **45** 123 (Jan) 1933 Poynton, F J, and Lightwood, R C Lymphatic Leukaemia, with Infiltration of Periosteum Simulating Acute Rheumatism, *Lancet* **1** 1192, 1932 Ehrlich, J C, and Forer, S Periosteal Ossification in Myelogenous Leukemia Report of Case Associated with Acute Rheumatic Fever, *Arch Int Med* **53** 938 (June) 1934 Snelling, Charles E, and Brown, Alan Bone Changes in Leukemia, *Clinical and Roentgenological*, *Arch Dis Childhood* **9** 315, 1934

379 Stephens, D J, and Bredeck, J F Aleukemic Myelosis with Osteosclerosis, *Ann Int Med* **6** 1087, 1932

380 Hirschfeld, H Ueber chronische Leukamien ohne Milz- und Lymphknotenvergrosserung, *Med Klin* **28** 1160, 1932

381 Jordan, A, and Schamschin, W Hautveränderungen bei aleukamischer Lymphadenose, *Dermat Ztschr* **66** 1, 1933 MacKenna, R M B, and Davie, T B Lymphatic Leukaemia with Cutaneous Manifestations, *Lancet* **1** 1196, 1932 Artz, L Leukamische Erkrankungen der Haut, *Wien klin Wchnschr* **46** 1125, 1933 Bykova, O Retikulo-endotheliale Leukosen (Mit Affektion der Haut), *Folia haemat* **51** 96, 1933 Frank, T J F Case of Acute Lymphatic Leukaemia with Leukaemia Cutis and Leucimides, *M J Australia* **1** 126, 1934 Hollander, L, Kastlin, G J, Permar, H H, and Schmitt, C L Myeloid Leukemia with Cutaneous Manifestations, *Arch Dermat & Syph* **29** 821 (June) 1934 Svdenstricker, V P, and Phinzy, T B Acute Monocytic Leukemia, A Case with Partial Autopsy, *Am J M Sc* **184** 770, 1932

aleukemic lymphadenosis of the orbit, orbital tumor,<sup>382</sup> labyrinthine lesion with acute otitis media and mastoiditis, mediastinal tumor, causing deafness, herpes zoster,<sup>383</sup> exophthalmos,<sup>384</sup> acute appendicitis with rupture,<sup>385</sup> a condition simulating appendicitis, ascites,<sup>386</sup> and aphonia<sup>387</sup> Leukemic infiltrations and hemorrhages in the central nervous system may cause symptoms such as bilateral facial paralysis<sup>388</sup> and papilledema<sup>389</sup> Stomatitis after the extraction of a tooth may be the first intimation of the presence of the disease<sup>390</sup>

In the absence of a blood picture suggesting leukemia, Baldrige and Barer<sup>391</sup> suggested the following criteria for aleukemic myelosis

- 1 Severe unexplained anemia with a color index of about 1 and with a moderate increase in reticulocytes
- 2 Hemorrhagic purpura which does not respond to transfusions of blood
- 3 Tumefaction of the gums
- 4 Unexplained enlargement of the spleen or lymph nodes
- 5 Symptoms of arthritis without selective atrophy of the muscles, increased tendon reflexes or palpable changes in the joints
- 6 Painful nerve roots or deep bony pain
- 7 Lytic lesions in bones (for example, lesions of the ribs seen in a roentgenogram of the chest)

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382 Cohen, M Orbital Lymphoma in Chronic Lymphatic Leukemia Report of Case, *Arch Ophth* **11** 617 (April) 1934

383 Haack, K Zoster Generalisatus bei lymphatischer Leukämie, *Dermat Wchnschr* **95** 1819, 1932 Craver, L F, and Haagensen, C D Note on Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma and Leukemias, *Am J Cancer* **16** 502, 1932

384 Reese, A B, and Guy, L Exophthalmos in Leukemia, *Am J Ophth* **16** 718, 1933

385 Rose, B H Acute Ruptured Appendicitis Complicating Chronic Leukaemic Myelosis, *New York State J Med* **33**.195, 1933

386 Cheney, G Chronic Myelogenous Leukemia with Ascites Resembling Banti's Syndrome With Report of Two Cases, *Acta med Scandinav* **81** 14, 1934

387 Stinson, W D Aphonia in Acute Leukemia, *J Tennessee M A* **27** 33, 1934

388 Garvey, P H, and Lawrence, J S Facial Diplegia in Lymphatic Leukemia, *J A M A* **101** 1941 (Dec 16) 1933 Howell, A, and Gough, J Acute Lymphatic Leukaemia with Facial Diplegia and Double Abducens Palsy, *Lancet* **1** 723, 1932

389 Hill, E Papilledema and Intracranial Complications of Leukemia, *Am J Ophth* **15** 1127, 1932 Hawksley, J C Lymphocytic Leukaemia Causing Pontine Haemorrhage, *Arch Dis Childhood* **7** 29, 1932 Olmer, J, and Alliez, J Les complications medullaires des leucémies, *Presse méd* **40** 1986, 1932

390 Sergeant and Laugier Stomatite apres avulsion dentaire, Signe revelateur d'une leucemie aigue, *Rev de stomatol* **35** 1, 1933

391 Baldrige, C W, and Barer, A Relationship Between Oxygen Consumption and Nitrogen Metabolism In Leukemia, *Arch Int Med* **51** 589 (April) 1933

- 8 Leukopenia with a shift to the left in an afebrile patient
- 9 Erythroblasts found unexpectedly in a smear
- 10 Pathologic fractures
- 11 High consumption of oxygen in a patient without fever or exophthalmic goiter
- 12 Unexplained acute enlargement of the breasts or ovaries

Of less moment are the following manifestations

- 1 Reddish-gray, nonliquefied tissue discovered at operation for osteomyelitis
- 2 Priapism
- 3 Abnormally high value for plasma globulin or fibrinogen
- 4 Unexplained hypercalcemia or hypocholesteremia
- 5 Bence-Jones' proteinuria
- 6 Abnormally rapid rouleau formation (Reimann)
- 7 Unexplained anticomplementary Wassermann tests

*Blood*—In 45 per cent of the cases of acute leukemia there may be a total count of less than 10,000 cells per cubic millimeter. The presence of blast and immature cells is essential in the diagnosis of leukemia of the leukopenic type (aleukemic leukemia)<sup>392</sup>. Heterophile agglutinins are confined to low titers, less than 1 to 4, serving as a differential feature from infectious mononucleosis<sup>393</sup>. The blood proteose is increased in chronic myelogenous leukemia and in acute leukemia, with variations in different stages of the diseases<sup>394</sup>. In tissue cultures of leukemic blood myeloblasts may develop into myelocytes, but the evidence that myelocytes mature into polymorphonuclear leukocytes or that erythrocytes mature from the more primitive forms is not definite<sup>395</sup>. The consumption of oxygen and glycolytic activity of leukocytes in normal and leukemic blood in vitro have been reported as inversely proportional to the concentration of the white blood cells<sup>396</sup> as opposed to previously reported observations that mature polymorphonuclear cells consume more oxygen under these conditions than the immature forms.

*Treatment*—A remission of six months after radium treatment and splenectomy has been reported in a case of myelogenous leukemia<sup>397</sup>.

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392 Watkins, C. H. Acute Leukopenic Leukemia and Its Differential Diagnosis, Wisconsin M. J. **32** 156, 1933

393 Bernstein, A. Diagnostic Importance of the Heterophile Anti-Body Test in Leukemia, J. Clin. Investigation **13** 677, 1934

394 Cooke, J. V. Proteolytic Leukocytic Enzyme in Leukemia, Study Made by Quantitative Method, Arch. Int. Med. **49** 836 (May) 1932

395 Pierce, M. Cultures of Leukemic Blood Leukocytes, Arch. Path. **14** 295 (Sept.) 1932

396 Soffer, L. J., and Wintrobe, M. M. The Metabolism of Leucocytes from Normal and Leukemic Blood, J. Clin. Investigation **11** 661, 1932

397 Carling, E. R., Carhill, H., and Pulvertaft, R. J. V. Splenectomy in Myeloid Leukaemia, Proc. Roy. Soc. Med. **26** 373, 1933

A remission of sixteen years following radiotherapy is recorded<sup>398</sup> Among the types of treatment, Jenkinson<sup>399</sup> suggested short wave irradiation over the anterior and posterior parts of the chest The entire spleen is not irradiated A soft spleen, even though enlarged, gives good results from treatment, but fever and a low hemoglobin content are unfavorable Phillips<sup>400</sup> reported good results from the use of a 4 Gm radium bomb Roentgen therapy does not cure the disease but may increase the efficiency of the patient at least 60 per cent<sup>401</sup> Different authors have recommended concentrated,<sup>402</sup> protracted<sup>401</sup> or small<sup>403</sup> treatments, depending on whether they considered that the roentgen rays cause cells to mature and die of senility<sup>402b</sup> or kill them in the stage in which they are irradiated A case has been reported<sup>404</sup> of aleukemic lymphatic leukemia in which there was a high basal metabolic rate and in which an induction of a symptomatic and hematopoietic remission followed thyroidectomy Symptomatic improvement in a case of chronic lymphatic leukemia may follow the use of compound solution of iodine, with a decrease in the symptoms associated with an elevated basal metabolic rate<sup>405</sup> Among other types of treatment reported are teleroentgenotherapy,<sup>406</sup> sulphur pyrethotherapy, total irradiation<sup>407</sup> and lead therapy (leukosis in chickens)<sup>408</sup> The resump-

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398 Fiessinger, N, and Arnaudet, A Leucemie lymphoide à forme splénique pure en excellent état après 16 ans de traitement, *Sang* **6** 411, 1932

399 Jenkinson, E L Myelogenous Leucemia, *Am J Roentgenol* **29** 91, 1933

400 Phillips, G W Myeloid Leukaemia Treated with the Four-Gramme Radium Bomb, *Lancet* **1** 22, 1933

401 Leucutia, T Irradiation in Lymphosarcoma, Hodgkin's Disease and Leukemia Statistical Analysis, *Am J M Sc* **188** 612, 1934

402 Isaacs, R (a) Present Status of Study and Treatment of Leucemia, *J Lab & Clin Med* **17** 1006, 1932, (b) Maturing Effect of Roentgen Rays on Blood-Forming Cells, *Arch Int Med* **50** 836 (Dec) 1932

403 Orton, G H Importance of Small Dosage in X-Ray Treatment of Leukaemia, *Brit J Radiol* **6** 242, 1933

404 Dameshek, W, Berlin, D D, and Blumgart, H L Complete Ablation of Thyroid Gland in Case of Chronic Lymphatic Leukemia with Hypermetabolism, *New England J Med* **210** 723, 1934

405 Friedgood, H B Effect of Lugol's Solution on Chronic Lymphatic Leukemia and Its Bearing upon Pathogenesis of Exophthalmic Goiter, *Am J M Sc* **183** 515, 1932

406 Marchal, G, and Mallet, L Sur une nouvelle methode de radiothérapie dans le traitement des leucemies La teléroentgentherapie totale, *Bull et mem Soc med d hop de Paris* **49** 737, 1933

407 Ebbehøj, K Total Roentgen Irradiation in Therapy of Leukemias, *Hospitaltid* **76** 445, 1933

408 Zadik, P Erfolgreiche Behandlung der Hühnerleukose mit Blei (Ein Versuch die Tumornatur der Hühnerleukose ex juventute abzuleiten), *Folia haemat* **50** 460, 1933

tion of the use of solution of potassium arsenite is recommended <sup>409</sup> Some authors recommend interruption of pregnancy in leukemic patients, <sup>410</sup> although a normal baby may be born Transfusion of blood may produce a temporary remission, especially in a case of acute leukemia <sup>411</sup> Radiothorium alone or in combination with roentgen rays has been advocated <sup>412</sup> In susceptible persons the blood count may be influenced by amidopyrine <sup>413</sup>

Of the different stages of cell growth, the myelocytes and small lymphocytes appear most "sensitive" to roentgenotherapy because when these are the predominant cells in the blood stream irradiation reduces the blood count most effectively This may be interpreted, however, as not meaning sensitivity but merely indicating that the roentgen rays make a cell go through the next normal stage in its development The myelocytes mature into polymorphonuclear neutrophils, and the lymphocytes are excreted or destroyed as mature cells On the other hand, primitive blast cells divide more rapidly, filling the blood-forming organs and ultimately causing death of the patient <sup>414</sup>

#### XANTHOMATOSIS AND NIEMANN-PICK'S, SCHULLER-CHRISTIAN'S AND GAUCHER'S DISEASES

A very complete study of the anomalies of lipid metabolism (essential primary xanthomatosis, Niemann-Pick's disease, Schuller-

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409 Forkner, C E Administration of Solution of Potassium Arsenite in Treatment of Chronic Myelogenous Leukemia, *M Clin North America* **15** 1057, 1932

410 Hofstein, J La leucemie comme indication d'interruption de la grossesse, *Strasbourg med* **91** 611, 1931, *Gynec et obst* **25** 45, 1932 Kaplan, I I, and Connery, J E Pregnancy in Course of Leukemia Case Report, *Am J M Sc* **183** 209, 1932 Neumann, H O Die myeloische Leukamie als Indikation zur Schwangerschaftsverhütung, *Deutsche med Wschnschr* **58** 292, 1932 Russell, H K Lymphatic Leucemia and Pregnancy, *Am J Obst & Gynec* **25** 493, 1933

411 Weil, P E, and Isch-Wall, P Un cas de leucemie lymphatique a pousse aigue avec anemie hyperchrome grave arrêtee par les transfusions sanguines, *Sang* **7** 204, 1933

412 Zadek, I Radiothorium bei leukamischer Myelose (kleine Dosierungen), *Folia haemat* **50** 161 and 369, 1933, **51** 1, 1933, Radiothorium bei leukamischer Myelose Grosse Dosierungen, *ibid* **49** 115, 1933, Tierexperimentelle Ergebnisse mit dem zur Behandlung der Leukamie verwendeten Radiothorium Reinjektionen, Kombinationen mit Rontgenstrahlen, *ibid* **48** 279, 1932

413 (a) Terry, M C, and Sanders, A O A Case of Myeloid Leukemia Treated with Luminal and Amidopyrine, *Proc Soc Exper Biol & Med* **31** 1154, 1934 (b) Isaacs, R Relation of Cell Types in Leukemia to Sensitivity to Radiation, *Folia haemat* **52** 414, 1934

414 Footnotes 402 b and 413 b

Christian's disease and Gaucher's disease) has been made by Rowland,<sup>415</sup> and others<sup>416</sup>

#### AGRANULOCYTOSIS

In November 1922 Schultz<sup>417</sup> described what he considered to be a new clinical syndrome, which he called agranulocytosis. The characteristics of this condition as described by him were ulcerative angina, marked reduction in or disappearance of the granulocytes from the peripheral blood, extreme prostration and frequently a rapidly fatal course. In the following year Friedemann<sup>418</sup> first applied the name agranulocytic angina to the condition. In addition to these names, other terms, such as granulopenia, granulocytopenia, malignant neutropenia and malignant leukopenia, have been introduced. The first case in the United States that was recognized as representing a distinct clinical entity, which was reported under the name of agranulocytic angina, is credited to Lovett,<sup>419</sup> whose report appeared in November 1924. In 1902, twenty-two years before, however, Brown reported a case<sup>420</sup> with observations on the blood which appeared to be an example of this syndrome.

Since the report of Schultz and especially in the past few years the condition appears to be increasing in frequency. Roberts and Kracke<sup>421</sup> stated that it has been reported in many countries throughout the world. The greatest incidence appears to be in Germany and the United States. These observers summarized reports of over 400 cases in the former country and of 473 cases in the latter. It is exceedingly difficult to estimate the true incidence of the disease, first, because an unknown number of cases are not recognized owing to the lack of an examination of the blood and, second, because all cases in which there is marked leukopenia cannot be classified as instances of true

415 Rowland, R. S. Anomalies of Lipid Metabolism (Constitutional Pathologic Lipoidosis), in Christian, H. A., and Mackenzie, J. Oxford Medicine, New York, Oxford University Press, 1931, vol. 4, chap. 7 A, 214 (3) and 214 (109) Oct. 1, 1931.

416 Knox, R. A., and Ramsey, G. W. Niemann-Pick's Disease (Essential Lipoid Histiocytosis), *Ann Int Med* **6** 218, 1932. Pick, Ludwig. Niemann-Pick's Disease and Other Forms of So-Called Xanthomatosis (Durham Lecture), *Am J M Sc* **185** 601, 1933.

417 Schultz, W. Ueber eigenartige Halserkrankungen (a) Monozytenangina, (b) Gangraneszierende Prozesse und Defekt des Granulozytensystems, *Deutsche med Wchnschr* **48** 1495, 1922.

418 Friedemann, V. Ueber Angina Agranulocytotica, *Med Klin* **19** 357, 1923.

419 Lovett, B. R. Agranulocytic Angina, *J A M A* **83** 1498 (Nov. 8) 1924.

420 Brown, P. K. A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leucopenia, *Am Med* **3** 649, 1902.

421 Roberts, S. R., and Kracke, R. R. Further Studies on Granulopenia with a Report of Twelve Cases, *Ann Int Med* **8** 129, 1934.

agranulocytosis For example, Doan <sup>422</sup> stated that only 20 per cent of the patients with leukopenia referred to his clinic have true agranulocytosis

It should be emphasized that extreme leukopenia may occur secondary to sepsis in cases of various diseases of the blood, such as aplastic anemia, aleukemic leukemia and pernicious anemia, and in certain cases following the therapeutic use of arsenic and gold preparations and after exposure to benzene Leukopenia which occurs in association with any of the foregoing conditions cannot be regarded as true agranulocytosis but, as Fitz-Hugh and Comroe <sup>423</sup> stated, is a "mere hematological manifestation" of some other disease

Roberts and Kracke <sup>421</sup> described a mild form of chronic granulopenia which occurs commonly in women between the ages of 40 and 60 years They stated that the patients have vague complaints such as weakness, exhaustion and fatigue It is difficult to state what relationship, if any, this condition has to true agranulocytosis, if it is granted that the former syndrome does occur

In referring to agranulocytosis of the Schultz type, Jackson and Parker <sup>424</sup> concluded that the "hematological picture, clinical course and pathological findings probably entitle it to a consideration as an entity" This appears to express adequately the opinion of a great majority of observers who have studied the condition

*Etiology*—Roberts and Kracke <sup>421</sup> have presented a logical theory concerning the mechanism of the production of the disease, as follows First, there is the onset in the bone marrow with a failure of myelocytic function This may be due to myelocytic aplasia or cessation of maturation (maturation arrest) The latter view is held by Fitz-Hugh and Krumbhaar <sup>425</sup> Second, after a few days there is an onset in the blood stream with a gradual diminution of the granulocytes until the number is greatly reduced or they completely disappear Third, there is the clinical onset, with the appearance of the characteristic symptoms Fourth, with a loss of protection, bacterial invasion begins Fifth, recovery or death follows

The initial cause of the failure of the bone marrow to produce granulocytes is not clearly understood It has been held by Brogsitter, <sup>426</sup>

422 Doan, C A Studies on Etiology and Treatment of Neutropenic States, J A M A **101** 2074 (Dec 23) 1933

423 Fitz-Hugh, T, Jr, and Comroe, B I Agranulocytic Angina (Pernicious Leukopenia), Am J M Sc **185** 552, 1933

424 Jackson, H, Jr, and Parker, F, Jr Agranulocytosis Its Etiology and Treatment, New England J Med **212** 137, 1935

425 Fitz-Hugh, T, Jr, and Krumbhaar, E B Myeloid Cell Hyperplasia of the Bone Marrow in Agranulocytic Angina, Am J M Sc **183** 104, 1932

426 Brogsitter, A M, and von Kress, H Ueber die "Agranulocytose" Krankheit Eine Kritik der Kasuistik und eigene klinische Beobachtungen, Virchows Arch f path Anat **276** 768, 1930

Lovett <sup>429</sup> and many others that the condition was due to severe sepsis. It is now thought that the sepsis is secondary to the condition rather than the primary cause of it <sup>427</sup>. It has been suggested that the initial cause is allergic, <sup>428</sup> others consider that it is an endocrine disturbance <sup>429</sup>. Recently it has been emphasized that the disease may be due to the administration of some therapeutic agent to a person who is susceptible to its action. Granulocytopenia has been observed following the use of arsphenamine and gold salts <sup>430</sup>. Kracke <sup>431</sup> emphasized that certain coal tar drugs may be of importance in the production of the disease, and more recently di-nitrophenol has been reported as an apparent cause of the condition <sup>432</sup>.

An important contribution bearing on the etiology of agranulocytosis was made by Madison and Squier <sup>433</sup> who, in October 1933, reported before the Central Society of Clinical Research certain observations which indicated that amidopyrine might precipitate the syndrome in certain susceptible persons. They reported <sup>434</sup> cases in 14 persons who had taken amidopyrine immediately before the onset of the disease.

427 Jackson, H, Jr. Agranulocytic Angina and Allied Conditions, *Internat Clin* **3** 68, 1933. Footnote 421.

428 Pepper, O. H. P. Leucopenia. A Review with Special Reference to Agranulocytic Angina, *California & West Med* **35** 173, 1931.

429 Baldrige, C. W., and Needles, R. J. Idiopathic Neutropenia, *Am J M Sc* **181** 533, 1931. Thompson, W. P. Observations on the Possible Relation Between Agranulocytosis and Menstruation with Further Studies on a Case of Cyclic Neutropenia, *New England J Med* **210** 176, 1934. Hubble, D. Influence of Endocrine System in Blood Disorders, *Lancet* **2** 113, 1933.

430 Achard, C., Coste, F., and Cahen, R. A propos des desordres hematologiques provoques par les sels d'or, *Bull et mem Soc med d hôp de Paris* **48** 547, 1932. Ameuille and Brailon. Sept cas de syndromes agranulocytaires auriques, *ibid* **48** 1627, 1932. Angéras and Ginsbourg. Aleucie hemorrhagique (agranulocytose) post-chrysotherapique, *Sang* **6** 798, 1932.

431 Kracke, R. R. Experimental Production of Agranulocytosis, *Am J Clin Path* **2** 11, 1932. Kracke, R. R., and Parker, F. P. The Etiology of Granulopenia (Agranulocytosis) with Particular Reference to Drugs Containing the Benzene Ring, *J Lab & Clin Med* **19** 799, 1934.

432 Bohn, S. S. Agranulocytic Angina Following the Ingestion of Dinitrophenol, *J A M A* **103** 249 (July 28) 1934. Davidson, E. N., and Shapiro, M. Neutropenia Following Dinitrophenol, with Improvement After Pentnucleotide Therapy and Leukocyte Cream, *ibid* **103** 480 (Aug 18) 1934. Dameshek, W., and Gargill, S. L. Studies in Agranulocytosis. Report of Two Cases of Agranulocytosis Following Use of Dinitrophenol, *New England J Med* **211** 440, 1934. Silver, S. New Danger in Dinitrophenol Therapy. Agranulocytosis with Fatal Outcome, *J A M A* **103** 1058 (Oct 6) 1934.

433 Madison, F. W., and Squier, T. L. Primary Granulocytopenia After Administration of Benzene Chain Derivatives, *J A M A* **101** 2076 (Dec 23) 1933.

434 Madison, F. W., and Squier, T. L. The Etiology of Primary Granulocytopenia (Agranulocytic Angina), *J A M A* **102** 755 (March 10) 1934.



Their observations have been confirmed by Watkins,<sup>435</sup> Randall,<sup>436</sup> Hoffman and his associates,<sup>437</sup> Sturgis and Isaacs<sup>438</sup> and others. The fact that a person ingests a certain drug immediately before the onset of a disease is suggestive but not conclusive evidence that it is the cause of the condition. The strongest evidence in support of this view is that Madison and Squier, Sturgis and Isaacs and Plum<sup>439</sup> produced leukopenia in patients who had recovered from agranulocytosis promptly after small doses of amidopyrine were administered. The relationship between amidopyrine and agranulocytosis has been studied by the Council on Pharmacy and Chemistry of the American Medical Association<sup>440</sup> with the conclusion that there is "no question that amidopyrine is very important in the production of granulocytopenia." Plum<sup>439</sup> has reviewed comprehensively the relation of amidopyrine to this condition and states that since May 1933, 128 cases have been reported in which agranulocytosis developed after therapeutic doses of amidopyrine. It should be emphasized, however, that it is not the sole cause of the condition, as Seeman<sup>441</sup> and Jackson<sup>442</sup> have reported a group of cases in which there was definitely no history of such therapy. It is possible that in some of the cases in which the patient reported that he had not taken amidopyrine as such, he may have taken it in combination with a barbiturate or some other drug under a trade name which gave no indication as to the nature of the medication.

*Observations on the Blood*—No attempt will be made to discuss the complete blood picture of the disease. It is sufficient to say that the most striking characteristic is a marked reduction or complete disappearance of the granulocytes from the peripheral blood. As the disease progresses the total leukocyte count may be as low as 300 per cubic

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435 Watkins, C. H. The Possible Rôle of Barbiturates and Amidopyrin in Causation of Leucopenic States, *Proc. Staff Meet., Mayo Clin.* **8** 713, 1933.

436 Randall, Clyde L. Severe Granulopenia Following the Use of Barbiturates and Amidopyrine. Report of Case, *J. A. M. A.* **102** 1137 (April 7) 1934.

437 Hoffman, A. M., Butt, E. M., and Hickey, N. G. Neutropenia Following Amidopyrine, Preliminary Report, *J. A. M. A.* **102** 1213 (April 14) 1934.

438 Sturgis, C. C., and Isaacs, R. Observations Concerning the Etiology of Agranulocytosis, *Tr. A. Am. Physicians* **46** 328, 1934.

439 Plum, P. Agranulocytosis Due to Amidopyrine, *Lancet* **1** 14, 1935.

440 Reznikoff, P. The Relation of Amidopyrine and the Barbituric Acid Derivatives to Granulocytopenia, Special Report to the Council on Pharmacy and Chemistry of the American Medical Association, *J. A. M. A.* **102** 2183 (June 30) 1934. This article contains a bibliography on the relation of amidopyrine to agranulocytosis.

441 Seeman, H. Amidopyrine as Etiological Factor in Agranulocytosis, *Ugeskr. f. læger* **96** 241, 1934.

442 Jackson, H., Jr. Relation of Amidopyrine and Allied Drugs to Etiology of Agranulocytic Angina, *Am. J. M. Sc.* **188** 482, 1934.

millimeter, which indicates that in addition to the granulocytes the lymphocytes and monocytes are diminished. An important point with regard to the blood is that in agranulocytosis there is rarely, if ever, a significant degree of anemia. When this is present it usually indicates that the leukopenia is associated with some other disease.<sup>424</sup>

A controversial point in regard to the blood picture concerns the blood platelets. A majority of observers<sup>443</sup> agree that the number of platelets is normal during the acute attack and is often increased as improvement begins. On the other hand, others<sup>444</sup> believe that the number is reduced. Kracke and Roberts<sup>421</sup> stressed that a hemorrhagic tendency is common in the disease, whereas most observers<sup>445</sup> have stated that this finding is rare.

*Treatment*—Therapeutic indication in this disease is obviously to increase the number of granulocytes in the peripheral blood, and various measures have been introduced in an attempt to accomplish this. The following therapeutic agents have been used: Nonspecific therapy, stimulating doses of roentgen rays,<sup>446</sup> sepsis and necrosis,<sup>421</sup> liver extract,<sup>447</sup> adenine sulphate,<sup>448</sup> pentnucleotide,<sup>449</sup> transfusions of blood<sup>450</sup> and leukocytic cream.<sup>451</sup>

443 (a) Kastlin, G. J. Agranulocytic Angina, *Am J M Sc* **173** 799, 1927. (b) Schultz, W., and Jacobowitz, L. Agranulocytosis, *Med Klin* **21** 1642, 1925. Millman, M., and Furcolo, C. L. Relapsing Agranulocytosis with Case Report, *New England J Med* **208** 440, 1933.

444 Aubertin, C., and Levy, R. L'agranulocytose et les syndromes agranulocytaires, *Arch d mal du coeur* **21** 369, 1928. Footnote 421.

445 Lichtenstein, A. Agranulozytose (Typus Schultz) (Granulocytopenia maligna), *Acta med Scandinav (supp)* **49** 1, 1932. Footnote 443a.

446 (a) Friedemann, U., and Elkeles, A. Die Roentgenbehandlung der Agranulozytose, *Deutsche med Wchnschr* **56** 947, 1930. (b) Taussig, A. E., and Schnoebelen, P. C. Roentgen Treatment of Agranulocytosis, *J A M A* **97** 1757 (Dec 12) 1931.

447 Foran, F. L., Sheaff, H. M., and Trimmer, R. W. Agranulocytic Angina. Treatment by Use of Parenteral and Oral Liver Extract, Preliminary Report, *J A M A* **100** 1917 (June 17) 1933. Coggeshall, L. T. Neutropenia, "Agranulocytic Angina", Report of Cases and Treatment, *M Clin North America* **17** 1645, 1934. von Bonsdorff, B. Lebertherapie bei Granulocytopenia, *Klin Wchnschr* **13** 1079, 1934.

448 Resnikoff, P. Adenine Sulphate Treatment of Agranulocytosis, *J Clin Investigation* **12** 45, 1933.

449 Jackson, H., Jr., Parker, F., Jr., and Taylor, F. H. L. Studies of Diseases of Lymphoid and Myeloid Tissues. Nucleotide Therapy of Agranulocytic Angina, Malignant Neutropenia and Allied Conditions, Analysis of Sixty-Nine Cases, *Am J M Sc* **184** 297, 1932.

450 Hueber, W. Beitrag zur Frage der Agranulozytose, *Frankfurt Ztschr f Path* **40** 312, 1930. Footnote 428.

451 Strumia, M. M. The Effect of Leukocytic Cream Injections in the Treatment of the Neutropenias, *Am J M Sc* **187** 527, 1934.

The evaluation of therapy in this disease is difficult, and anything which is said in regard to this at present must be tentative. This is because spontaneous recovery does occur in the disease, the patient who is treated may have secondary granulocytopenia instead of true granulocytosis, and drugs which have a deleterious effect, such as amidopyrine, may be administered simultaneously with the therapeutic agent. In brief, it may be said that roentgen treatment should be used with great caution because there may be an initial depression of the bone marrow before a stimulating effect occurs.<sup>452</sup> There is no convincing evidence that liver extract, nonspecific therapy, adenine sulphate or leukocytic cream is of therapeutic value. Multiple small transfusions of blood may be beneficial. There is no conclusive proof that they depress the bone marrow. There are more data in support of the effectiveness of pentnucleotide therapy than of any other form of treatment. In a group of 103 patients treated with this drug Jackson<sup>424</sup> reported a mortality of 33 per cent, as compared with a mortality of 76 per cent in a group of untreated patients reports of whose cases were compiled from the literature by Taussig and Schnoebelen,<sup>446b</sup> of 77 per cent as given by Brogsitter<sup>426</sup> and of 77 per cent as reported by Uffenorde.<sup>453</sup> Jackson and Parker<sup>424</sup> concluded that "at the present writing it would seem that pentnucleotide, provided there are no untoward reactions, offers the best chance of recovery in a patient with true agranulocytosis."

### HEMATOLOGIC TECHNIC

A detailed account of progress in technic is out of place in a review devoted to the broader concepts of hematology. Brief mention will be made of a few methods and procedures of special interest without an attempt to furnish a complete bibliography.

In the study of the blood in cases of anemia increasing emphasis has been placed on correlation of the erythrocyte count, the hemoglobin level and the size of the erythrocytes. Although the value of such quantitative relationships was emphasized by Gram and Norgaard and Haden in 1923, they received little attention before the stimulation of interest in hematologic diagnosis occasioned by the advances of the past decade. Classifications of anemia based on the number, size and hemoglobin content of the red blood cells have been devised by Haden,<sup>454</sup>

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452 Doan, Charles A. The Neutropenic State. Its Significance and Therapeutic Rationale, *J A M A* **99** 194 (July 16) 1932

453 Uffenorde, H. Ausgedehnte Nekrotisierungen des Verdauungsschlauches bei Agranulocytose nebst Bemerkungen über die ursächlichen Bedingungen dieser Erkrankung, *Virchows Arch f path Anat* **287** 555, 1932

454 Haden, R L. Clinical Significance of Volume and Hemoglobin Content of the Red Blood Cell, *Arch Int Med* **49** 1032 (June) 1932

Osgood and Haskins <sup>455</sup> and Wintrobe <sup>456</sup> Heller and Paul <sup>457</sup> have shown that the use, as an anticoagulant, or a mixture of ammonium oxalate, 6 parts, and potassium oxalate, 4 parts, does not alter the volume of the red cells. Two milligrams of the combined salts per cubic centimeter of blood are employed. This is an important contribution to the measurement of erythrocyte volume by the use in conjunction of the hematocrit value and the red cell count. Keller, <sup>458</sup> employing Bock's <sup>459</sup> modification of Pijpe's diffraction method, determined the mean diameter of the erythrocytes of a large series of normal persons and found the range of the group to be from 7.30 to 7.76 microns, the average being 7.6 microns. He studied the size of the red cells of persons with pernicious anemia and correlated it with the blood count and the response to treatment. Of 45 patients with tuberculosis he found slight macrocytosis in 20 by the diffraction method.

Increasing interest in the iron deficiency anemias has inspired a number of recent clinical studies of iron in the blood <sup>460</sup>. It has not been convincingly demonstrated that the determination of the iron content of the circulating blood supplements information gained from accurate estimations of the hemoglobin content. Its chief value, as Haden <sup>461</sup> stated, is as a substitute for the test of oxygen capacity in the standardization of hemoglobinometers <sup>462</sup>.

The Wright and Giemsa staining methods have retained their popularity in the study of the morphology of the white blood cells. The supravital technic aids in the differentiation of cells in some types of

455 Osgood, E. E., and Haskins, H. D. Causes, Classification and Differential Diagnosis of Anemias Based on Detailed Examination of Over Two Hundred Patients and Study of the Literature, *Ann Int Med* **5** 1367, 1932.

456 Wintrobe, M. M. Anemia. Classification and Treatment on Basis of Differences in Average Volume and Hemoglobin Content of Red Corpuscles, *Arch Int Med* **54** 256 (Aug.) 1934.

457 Heller, V. G., and Paul, H. Changes in Cell Volume Produced by Varying Concentrations of Different Anti-Coagulants, *J Lab & Clin Med* **19** 777, 1934.

458 Keller, H. R. Die klinische und praktische Bedeutung der Erythrocytendurchmesserbestimmung mit Hilfe der Diffraktionsmethode (Halometrie), unter besonderer Berücksichtigung der Perniciosa-Diagnose, *Ztschr f klin Med* **127** 132, 1934.

459 Bock, H. E. Neue Möglichkeiten praktischer Anamedagnostik (Ergebnisse der Erythrozytometrie), *Munchen med Wchnschr* **81** 1646, 1934.

460 Reich, C., and Tiedemann, V. G. Study of "Iron Volume Index" of Blood and Its Significance in Treatment of Anemia, *Am J M Sc* **184** 637, 1932. Dowden, C. W., and McNeill, C. Clinical Study of Blood Iron and Hemoglobin, *J Lab & Clin Med* **19** 362, 1934.

461 Haden, R. L. Determination of Hemoglobin by Iron Content Method, *J Lab & Clin Med* **19** 406, 1934.

462 Broun, G. O., and Briggs, A. P. Hemoglobin and Blood Cell Relations as Determined by Iron and Oxygen Capacity Methods, *J Lab & Clin Med* **19** 886, 1934.

leukemia, and it is especially applicable to the study of the monocyte response <sup>463</sup> The Schilling index or one of its modifications is of recognized value in the study of the response to infection <sup>464</sup> However, as Fitz-Hugh warned, <sup>465</sup> the information gained from its use is never more than suggestive and should be considered in relation to all other available data Estimation of the erythrocyte sedimentation rate has become an increasingly popular procedure Under controlled conditions it has definite value as an index of activity in pulmonary tuberculosis <sup>466</sup> and probably in rheumatic carditis <sup>467</sup> The sedimentation test has been advocated as a routine procedure in preventive medicine in schools and institutions <sup>468</sup>

In spite of its importance in a variety of hemorrhagic conditions the study of the blood platelets has been handicapped by a lack of technical procedures of easy application and proved worth Methods of enumeration of the platelets have been excellently reviewed by Olef, <sup>469</sup> who believes that greatest accuracy is obtained by the use of true indirect methods involving the determination of the ratio of platelets to erythrocytes He describes a technic of enumeration of the platelets based on this principle Blacher <sup>470</sup> has classified blood platelets according to size and staining characteristics He has made differential platelet counts

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463 Tompkins, E H Clinical Application of Supra-Vital Staining, *J Lab & Clin Med* **17** 921, 1932

464 Harkins, H N Present Status of Blood Examination in Diagnosis of Surgical Infections with Study of Twenty-Seven Indices of Infection Reported in Literature, *Surg, Gynec & Obst* **59** 48, 1934 Case, J W, Jr Schilling Differential Count and Red Cell Sedimentation Rate as Measurement of Activity in Pulmonary Tuberculosis, *New England J Med* **211** 252, 1934 Arvanitopulo, F T Study of Morphology of White Corpuscles of Blood in Prognosis of Operations, *Ann Surg* **100** 11, 1934 Rogatz, J L Schilling Blood Count as Aid in Diagnosis of Acute Appendicitis in Children, *J Pediat* **4** 757, 1934

465 Fitz-Hugh, T, Jr Age of Leucocyte in Relation to Infection, *J Lab & Clin Med* **17** 975, 1932

466 Ringer, P H, and Roach, M Blood Sedimentation Test Its Use as a Routine, Especially in Pulmonary Tuberculosis, *Ann Int Med* **8** 258, 1934 Thiele, G Ueber den Wert der Bestimmung der Blutkorperchensenkungsgeschwindigkeit fur die Diagnosen- und Prognosenstellung bei der Lungentuberkulose, *Beitr z Klin d Tuberk* **85** 302, 1934

467 Perry, C B Sedimentation Rate in Rheumatic Carditis, *Arch Dis Childhood* **9** 285, 1934

468 Gallagher, J R Value of the Blood Sedimentation Test in Routine Medical Examination of Adolescents and in Certain of Their Diseases, *Am J M Sc* **188** 450, 1934

469 Olef, I Enumeration of Blood Platelets, *J Lab & Clin Med* **20** 416, 1935

470 Blacher, L Recherches expérimentales sur les methodes d'exploration et sur la morphologie des thrombocytes ainsi que sur leur importance clinique en tant que systeme autonome, *Sang* **9** 147, 1935

on the blood of normal persons and in cases of anemias of different types, pulmonary tuberculosis, hyperthyroidism, Addison's disease, essential thrombocytopenic purpura and lymphatic leukemia. In these conditions he has found characteristic morphologic changes in the platelets as well as alterations in their total number.

A simplified procedure for obtaining sternal marrow in living persons consists of the introduction of a short needle with a thick bore at the sternomanubrial junction. A mixture of blood and bone marrow is readily obtained by aspiration and is suitable for the preparation of films stained by Wright's or, preferably, Giemsa's method. Young and Osgood<sup>471</sup> described the technic of this method, reported their observations from its use in health and in disease conditions and provided a complete bibliography. Reich<sup>472</sup> suggested that the fluid obtained by aspiration be centrifugated and films made from the buffy coat.

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471 Young, R. H., and Osgood, E. E. Sternal Marrow Aspirated During Life. Cytology in Health and in Disease, *Arch Int Med* **55** 186 (Feb.) 1935.

472 Reich, C. A Modified Technique for Sternal Puncture and Its Value in Hematologic Diagnosis, *J Lab & Clin Med* **20** 286, 1934.

## Book Reviews

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**A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease** By Arthur R Cushny Tenth edition, thoroughly revised by C W Edmunds and J A Gunn Price, \$6 50 Pp 786, with 75 illustrations Philadelphia Lea & Febiger, 1934

The title and introduction to this book seem to indicate a duality of subjects the one concerns pharmacology as a branch of biologic science, the other, as a method for the treatment of disease Pharmacology is defined as the study of changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods, it is further stipulated that the drug must be introduced from without The position of pharmacology in biologic science is described as follows "Thus as physiology is the study of the life of the normal organism, pharmacology is the study of the organism rendered abnormal by drugs, while in pathology the phenomena of life under disease are examined" It is also stated that all three subjects may be pursued without reference to the practical needs of medicine These delineations, in their present form, are not quite satisfactory Pharmacology surrenders too much territory, and whether a potent agent is introduced into the organism from without or is produced within the organism seems rather immaterial The anti-septic action of hydroxybutyric acid in infections of the urinary tract may be cited as a case in point Later, happily, it is stated that the action of drugs must be studied in the diseased as well as in the healthy organism

The reviewer grants that pharmacology need not concern itself solely with the practical needs of medicine, but considers that a greater intimacy is needed between pharmacology and medicine Such intimacy is to the advantage of both and so to the advantage of the sick And whatever else the goal may be, one cannot forget that the prevention, care and alleviation of sickness are the paramount issues of medicine, and that these issues largely determine the place of pharmacology in the medical school This has not always been seen too clearly, with the unfortunate result that pharmacology as an independent branch of instruction is endangered, greatly to the detriment of both medicine and of pharmacology

Thus the reviewer cannot emphasize too strongly, with the authors, that the great importance of pharmacology is not so much in its purely biologic aspects as in its significance in the treatment of disease, and that when the mode of action of a drug is understood much greater accuracy is attained in using it in treatment "The object of pharmacology is to provide a scientific foundation for therapeutics and to increase the resources of the art of healing" If the authors mean by "art of healing" medicine, one can agree, but it might be well to emphasize that what medicine needs badly is less art and more healing, and that one looks to pharmacology for assistance in this

Cushny's book has long been recognized as a standard text, so it is hardly necessary to state that it fully merits this revision by Edmunds and Gunn They have done well A few minor suggestions may be made For instance, in speaking of methenamine it might be stated that the urine must be acidified to a given  $pH$  and that this can be accomplished most readily by such salts as ammonium or calcium chloride When giving crystalline hexylresorcinol, care has to be taken not to burn the mouth The chapter on alcohol is singularly free from bias It is stated, however, that the observations of Kraepelin with regard to the measurements of intellectual work lose much of their importance from the fact that the subjects knew when alcohol had been given them The reviewer happened to be one of these subjects, and neither he nor his fellow subjects were influenced by suggestion This was excluded by the arrangement of the experiments Mild

mercurous chloride might still deserve a place among the purgatives, even if it is discussed under "Mercury" These are minor matters which in no way detract from the value of the book

At the end is a classification of drugs based on their therapeutic uses, a welcome arrangement which facilitates the orientation of the reader

The book can be recommended highly to both the student and the physician

**On the Ammonium Content of the Urine in Normal and Certain Pathologic Conditions, Especially in Patients with Convulsions** By Joergen Madsen Pp 215 Copenhagen Levin & Munksgaard, 1933

It appears from the literature that an abnormal acid-base equilibrium and an abnormal ammonia metabolism are frequently observed in cases of epilepsy. Controversial points are still under discussion. Madsen has limited his investigations to the urinary excretion of ammonia under varying conditions. He studied the  $p_H$  of the urine of normal persons and that of patients with convulsions and made the following observations. In patients who have convulsions, the average value for the  $p_H$  of the urine is higher and the variations from day to day are more marked. In normal persons, the daily range of the  $p_H$  of the urine is from below 6 in the morning to 7 later in the day. In patients with convulsions, the rise of the  $p_H$  in the latter part of the day is more marked. It almost always reaches alkaline values, a rare occurrence in normal persons. Alkali taken by mouth is more readily excreted in the urine of patients with convulsions than in that of normal persons.

Investigation of the excretion of ammonia in the urine revealed that the ammonium factor (the ammonium nitrogen-total nitrogen quotient) is, on the average, definitely increased in patients with convulsions and shows more marked variations from day to day than in normal persons. The excretion of ammonia was dependent on the  $p_H$  of the urine. Under normal conditions a rather constant relationship exists between the  $p_H$  and the ammonium nitrogen-total nitrogen quotient, and a somewhat less marked relationship between the  $p_H$  and the ammonium concentration of the urine. The ammonium nitrogen-total nitrogen quotient, as well as the total amount of ammonia excreted under conditions of constant urinary  $p_H$ , is higher in patients with convulsions than in normal persons.

Madsen discusses the so-called hyperbola regulation of Hasselbach, who found a relationship between the  $p_H$  of the urine and the ammonium nitrogen-total nitrogen quotient. The relationship is expressed by a hyperbolic curve. Madsen is in agreement with other authors in finding this hyperbolic regulation to be only approximately correct, however, the modified form of the hyperbola, the so-called regulation figure, gives the best expression at the present time for the relationship of the excretion of ammonia to the urinary  $p_H$ . In patients with convulsions, Madsen found increased values for the regulation figure.

The hyperammoniuria of persons with convulsions was not regularly accompanied by generalized acidosis. However, Madsen considers it possible that a disturbance of the acid-base equilibrium may be associated, since his investigations seem to indicate that the alkali in the tissues of the epileptic patient may be bound in some unusual manner so that at times retention of alkali occurs and at other times increased excretion. It is therefore assumed that the acid-regulating rôle of alkali is impaired in the organism of the epileptic person, resulting in the increased production of ammonia.

Madsen postulates a close relationship between hyperammoniuria and the precipitation of convulsions. Overventilation is more frequently followed by convulsions in patients with hyperammoniuria. Hyperammoniuria, it is assumed, is the result of an abnormality of metabolism which may be constitutional. It is understood that this is only one of the many factors of importance in the pathogenesis of convulsions.



**Allergy and Applied Immunology** A Handbook for Physician and Patient, on Asthma, Hay Fever, Urticaria, Eczema, Migraine and Kindred Manifestations of Allergy By Warren T Vaughan Second edition Price, \$5 Pp 420, with 40 illustrations St Louis C V Mosby Company, 1934

The appearance of a second edition of a book within three years of first publication is good evidence that it has been received with favor This is an excellent handbook for physician and patient on allergic conditions The subject is presented with a thoroughness and simplicity that make it readily understandable to the average layman An appendix of instructions, directions and forms has been added which should prove helpful in working out the causation of any particular case of allergy

This presentation is recommended as a practical guide in the care of allergic persons One can hardly praise it too highly

**Collens System of Diet Writing Including Diet Calculator** By William S Collens Price, \$5 New York Form Publishing Company, 1933

Assembled in a loose-leaf folder are calculating cards for rapidly figuring all sorts of diets, lists of foods according to their content of vitamins, minerals and other constituents, brief lists of diets for various diseases, and, finally, a pad of blanks for prescribing diets The reviewer is fascinated by the calculating cards By spinning a wheel or sliding cards in and out past slits one can instantly formulate an almost limitless variety of diets

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## News and Comment

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### NATIONAL ASSOCIATION FOR PREVENTION OF TUBERCULOSIS IN ENGLAND

The National Association for the Prevention of Tuberculosis of England will hold its twenty-first annual conference at Southport, June 27 to 29 The subject for discussion will be "The Responsibility of the Nation Toward the Child in Respect of Tuberculosis"

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### CORRECTION

In the article by Drs Necheles and Coyne, entitled, "Secretion of Mucus and Acid by the Stomach in Healthy Persons and in Persons with Peptic Ulcer," in the March issue (ARCH INT MED 55 395, 1935), "(P = 0 54)" in the fifth line of the fourth paragraph on page 399 should read "(P = 0 054)"

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